The Journal of the American Osteopathic Association

JANUARY 1960 • VOLUME 59

Metabolic acidosis

Educational supplement

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1. Muir, A., and Cossar: I. A., Brit. M. J. *2*:7-12 (July 2) 1955. 2. Waterson, A. P.: Brit. M. J. *2*:1531 (Dec. 24) 1955. 3. Brown, R. K., and Mitchell, N.: Gastroenterology *31*:198-203 (Aug.) 1956. 4. Kelly, J. J., Jr.: Am. J. Med. Sci. *232*:119-128 (Aug.) 1956. 5. Brick, I. B.: J. Am. Med. Assn. *163*:1217-1219 (April 6) 1957. 6. Trimble, G. X.: Correspondence, J. Am. Med. Assn. *164*:323-324 (May 18) 1957. 7. Lange, H. F.: Gastroenterology *33*:770-777 and 778-788 (Nov.) 1957. 8. Tebrock, H. E.: Ind. Med. & Surg. *20*:480-482, 1951. 9. Harrisson, J. W. E.; Packman, E. W., and Abbott: D. D.: J. Am. Pharm. Assn. (Scient. Ed.) *48*:50-56 (Jan.) 1959. 10. Paul, W. D.; Dryer, R. L., and Routh, J. L.: J. Am. Pharm. Assn. (Scient. Ed.) *39*:21 (Jan.) 1950.

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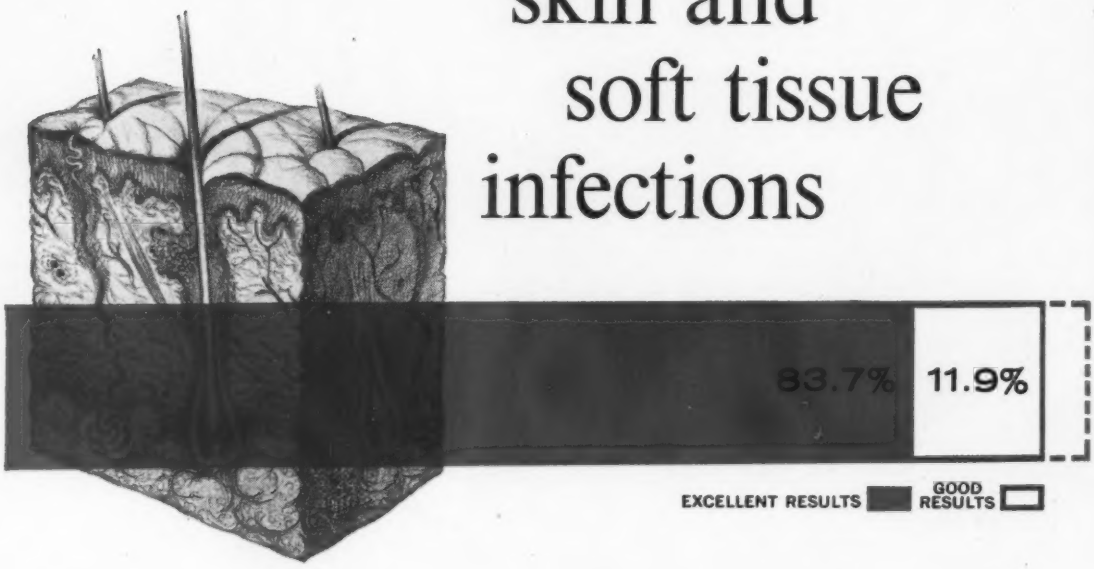

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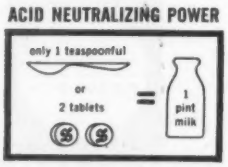

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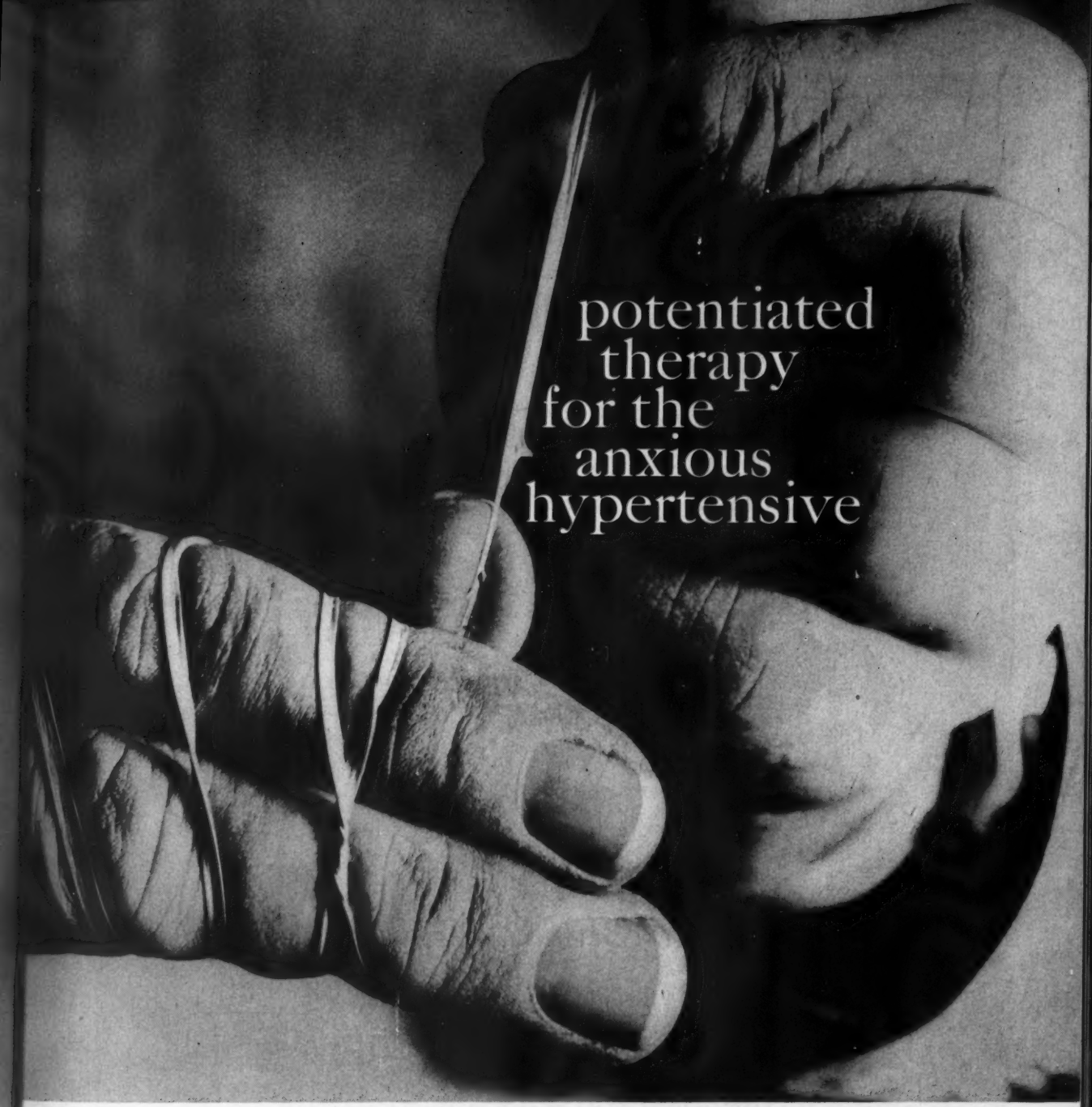

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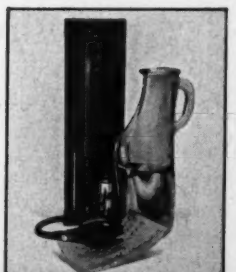

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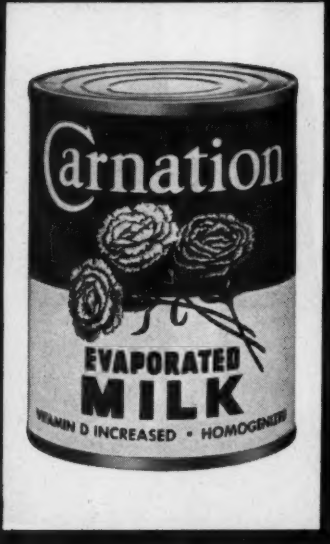

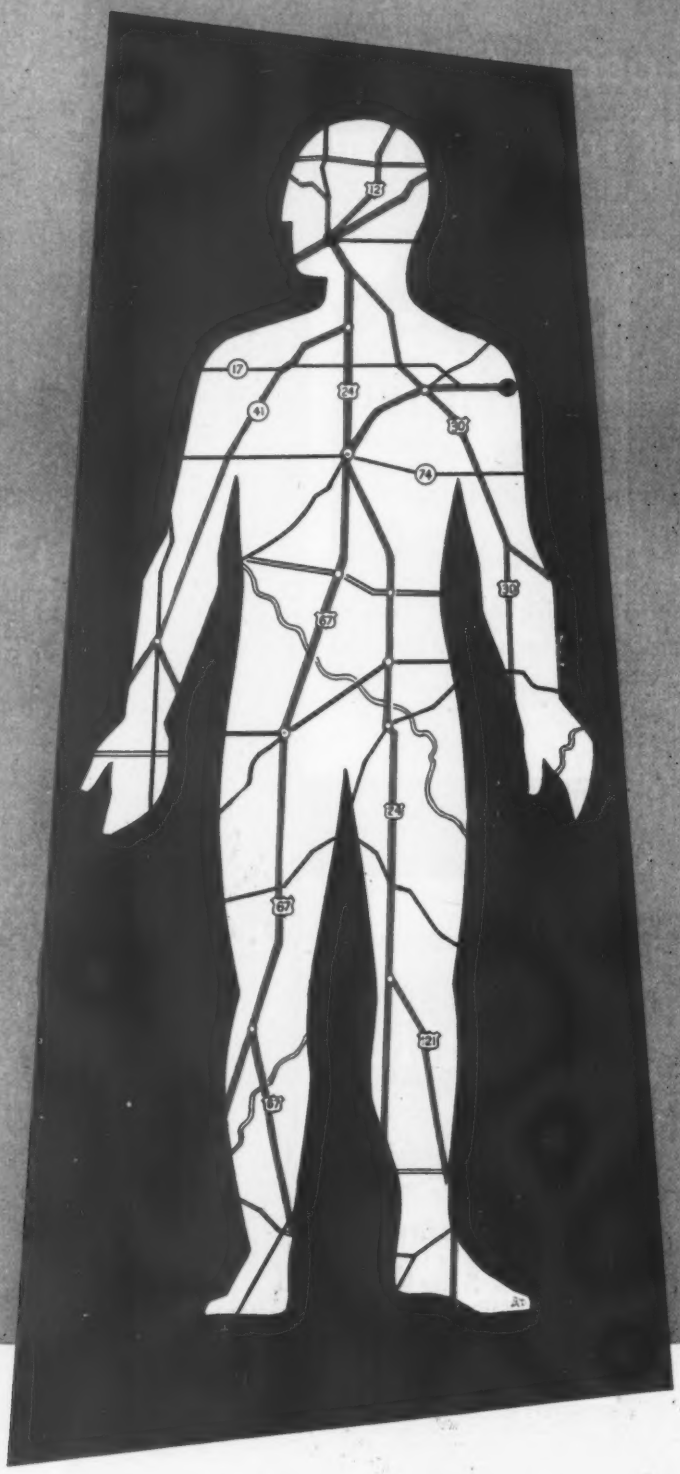

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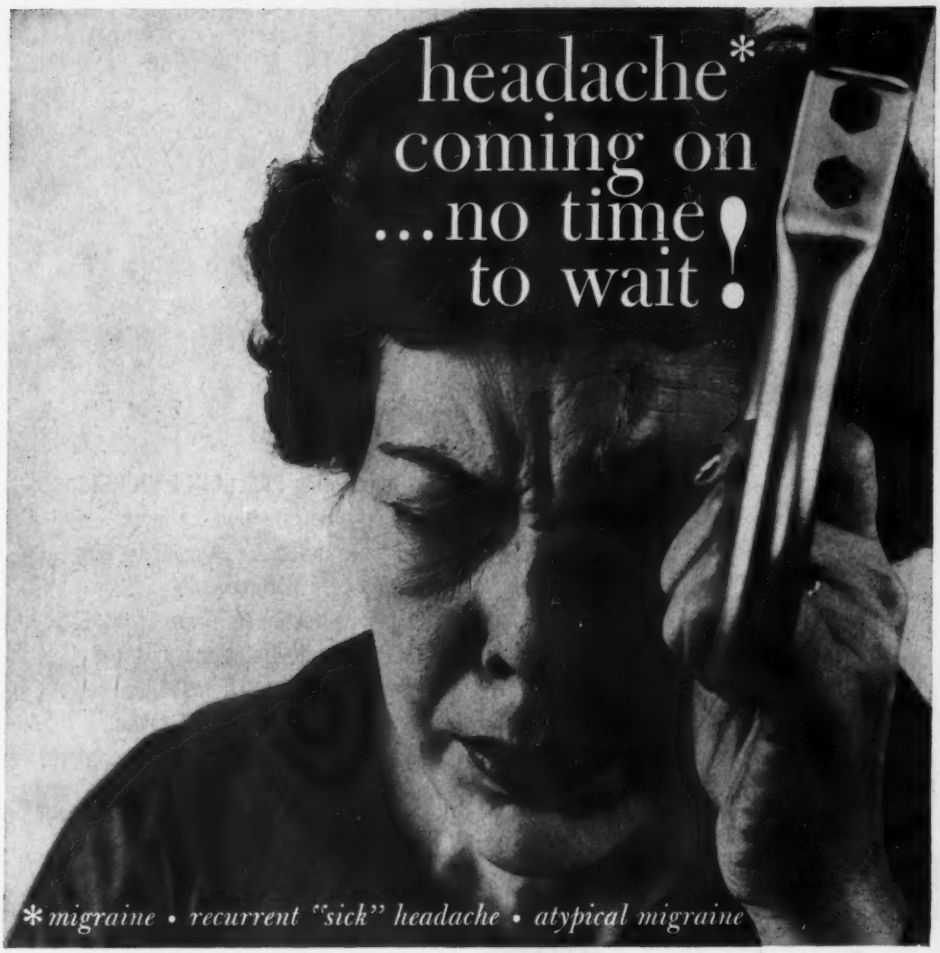

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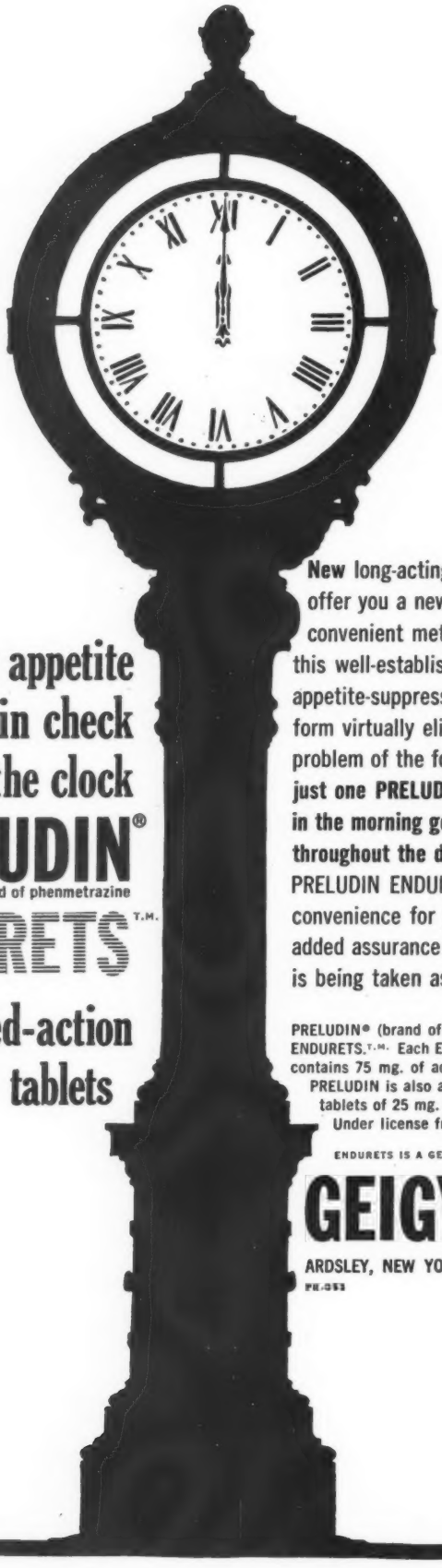

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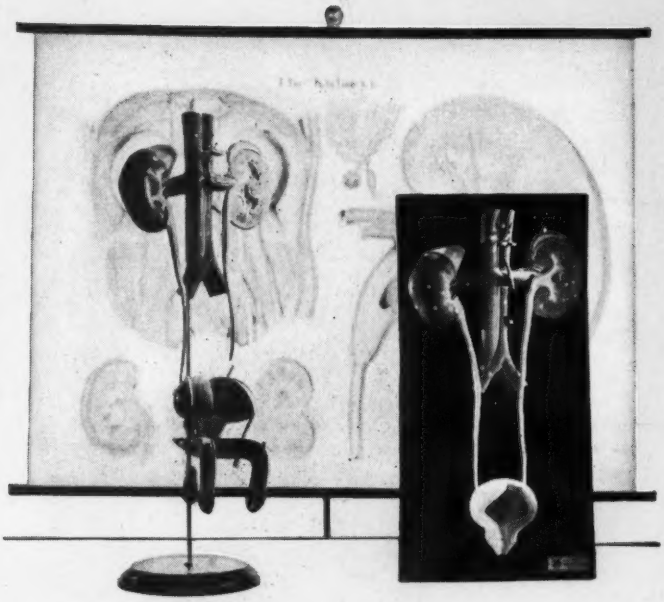

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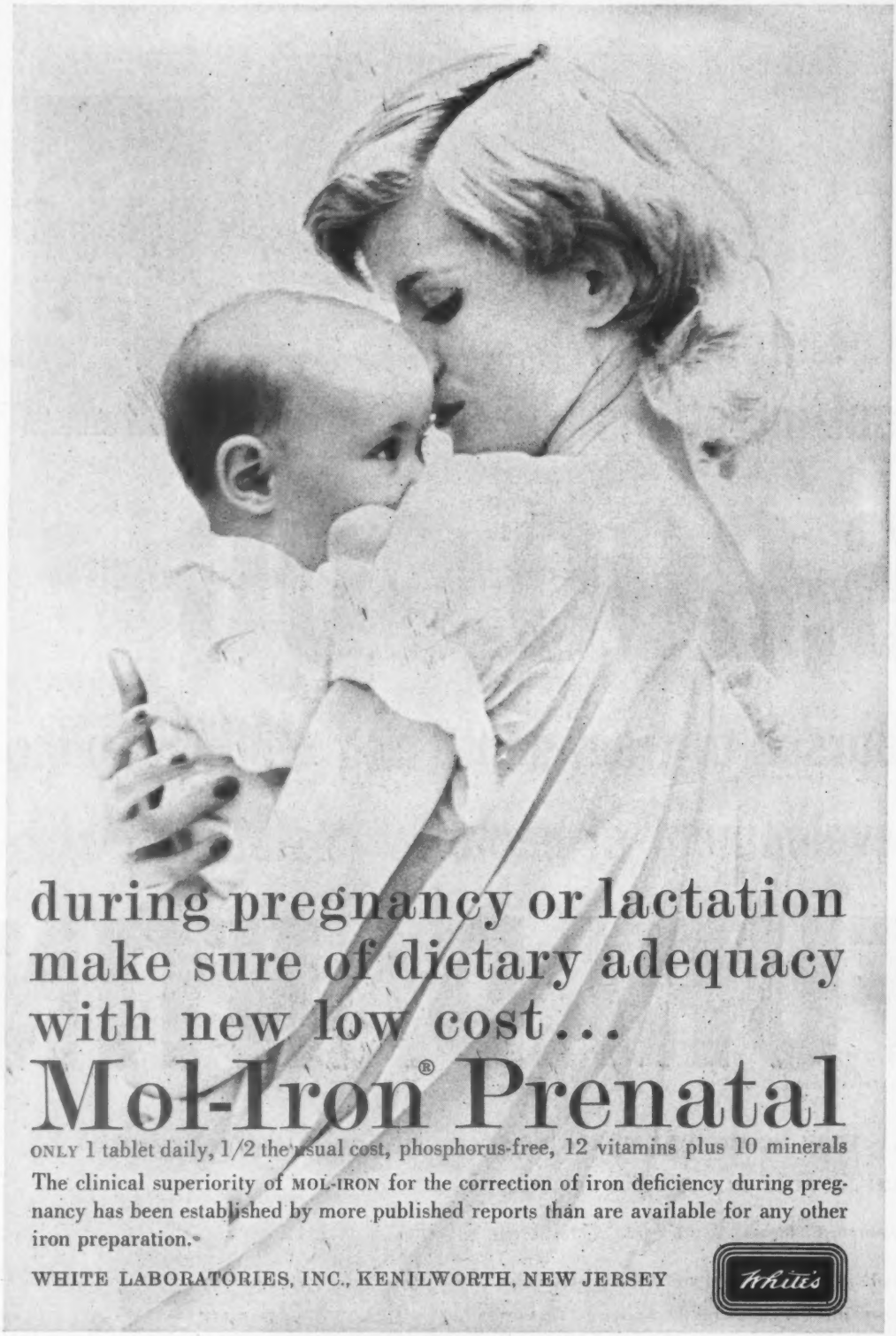

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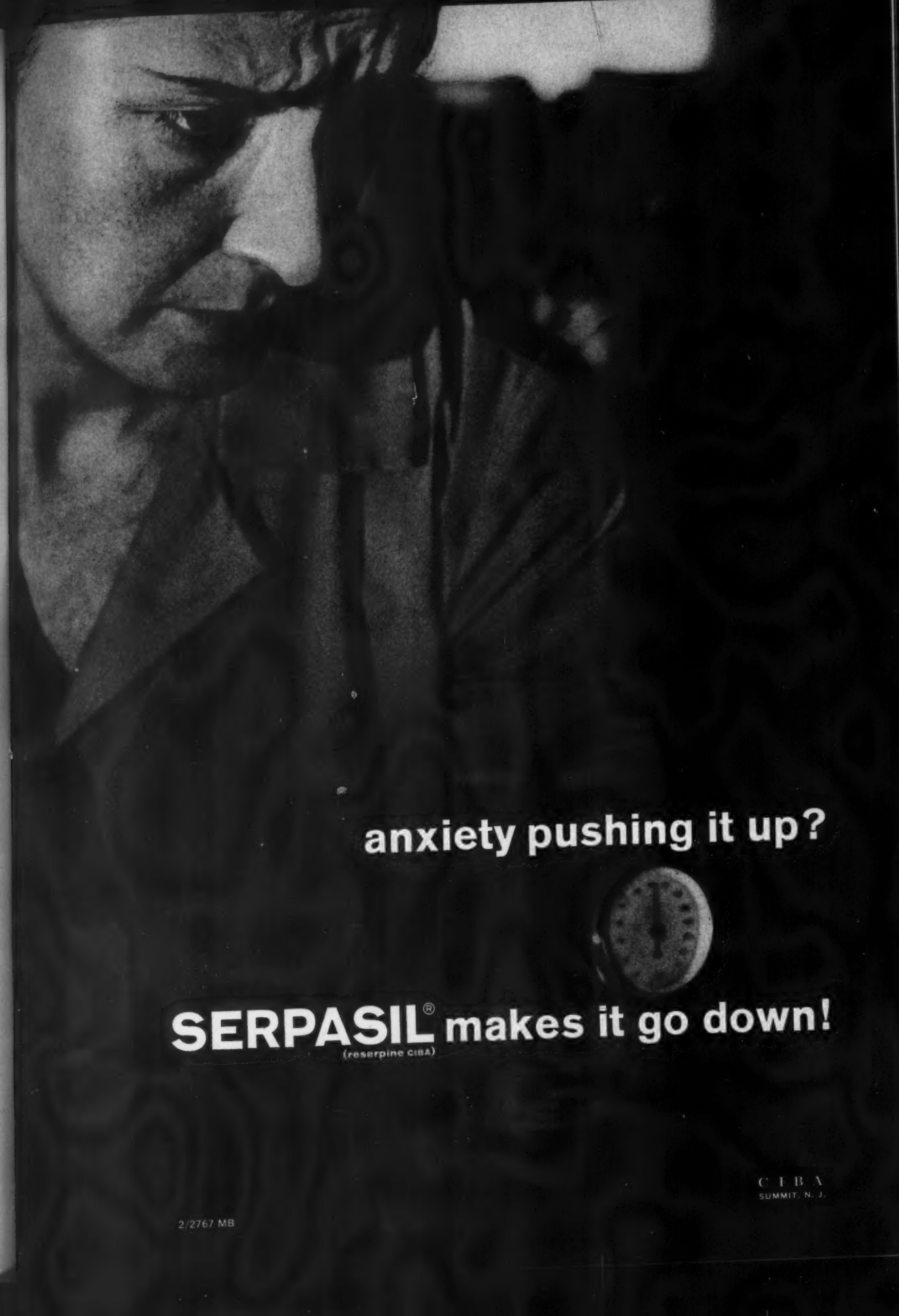
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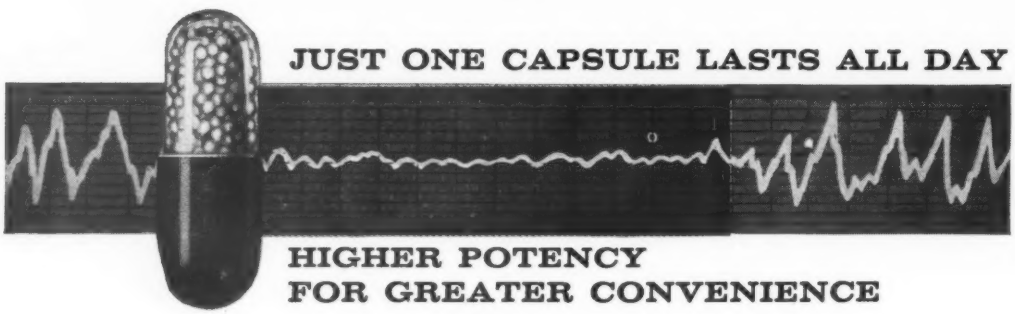

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Q

Shouldn't **KANTREX**® Injection* be kept in reserve for treating staph or gram-negative infections until other antibiotics have been tried first?

a

No. Naturally, KANTREX Injection should not be used in mild or self-limited infections, but as Yow states, "it should not be withheld in moderately severe or severe infections."[1]

Q *What properties of* KANTREX *led Yow to draw this conclusion?*

Next page, please . . .

*Kanamycin sulfate injection (Bristol)

MORE QUESTIONS on the clinical use of KANTREX®

Q *What properties of* KANTREX *led Yow to draw this conclusion?*

a The following[2]: (1) KANTREX Injection is bactericidal, not merely bacteriostatic; (2) it is absorbed rapidly after intramuscular injection; (3) it has proved successful in many types of staph and gram-negative infections resistant to other antibiotics; and (4) it is well tolerated when used judiciously.

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it?*

a Numerous investigators have reported that micro-organisms do not readily develop resistance to KANTREX in a clinical setting; and emergence of resistance to KANTREX has not been a practical problem.[3,4,5,6,7,8]

Q *How does the* in vitro *activity of* KANTREX *against staph compare with that of other antibiotics?*

a Griffith and Ostrander[9] tested 794 strains of staphylococci and found that 95.2% were sensitive to KANTREX. By contrast, only 15.5% of the same organisms were sensitive to penicillin, 33.5% to tetracycline, 52.4% to erythromycin, and 71.7% to chloramphenicol.

Q *What about the sensitivity of other pathogens to* KANTREX*?*

a Leming[10] recently summarized the *in vitro* activity of KANTREX against 4493 strains of various organisms isolated from hospital patients over a 7-month period. He reported that the following percentages of these clinical isolates were sensitive to KANTREX: *Proteus mirabilis*, 98%; *Proteus morganii*, 94%; *Proteus rettgeri*, 89%; *Proteus vulgaris*, 87%; *Paracolobactrum intermedium*, 96%; *Coli-aerogenes* group, 93%; *Streptococcus viridans*, 78%; *Salmonella* and *Shigella*, 92%.

Q *What do these figures mean clinically?*

a A great deal. As Yow stated in recent reviews of KANTREX Injection, it "appears to be one of the

most effective anti-staphylococcal antibiotics available today."[1,2] KANTREX Injection is also effective in the treatment of infections caused by "most strains of *E. coli, Proteus sp.*, the *Klebsiella pneumoniae-Aerobacter aerogenes* group, and many strains of *Pseudomonas aeruginosa* resistant to other antibiotics."[2] In another report, KANTREX Injection was placed at the head of the list of drugs "with the most chance of success" against *A. aerogenes* urinary tract infections.[11]

Q *Have these findings about* KANTREX *therapy been substantiated by other investigators?*

a Yes, indeed. Finegold,[12] who reviewed the clinical findings of 64 investigators, reported that infections which "usually responded" to KANTREX included: staph infections (including staph enteritis), *E. coli* infections (including *E. coli* gastroenteritis), atypical acid-fast bacillus infections, *Aerobacter-Klebsiella* infections, paracolon infections, *Alcaligenes* infections, *Shigella* dysentery, *Salmonella* enteritis, anthrax, amebiasis, and *E. histolytica* carrier state. Among the infections that "sometimes responded" were listed: pneumococcal infections, group A *beta*-hemolytic streptococcic infections, *Proteus* infections, gonorrhea, and paratyphoid fever.

Q *That's an impressive list. What didn't respond?*

a According to Finegold's tabulation, treatment failures were "usually" encountered in brucellosis, *Pseudomonas* infections, typhoid fever, mycotic infections and anaerobic infections.[12]

Q *How long do I have to give* KANTREX *Injection before I know whether it works or not?*

a Generally 2 or 3 days or less. Usually the effectiveness of KANTREX Injection can be determined in 24 to 36 hours. Rutenburg et al. reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[13]

Q *How long should I continue to administer* KANTREX?

a If definite clinical response does not occur within 5 days, KANTREX therapy should be stopped and the antibiotic sensitivity of the invading organism rechecked.

Q *What is the hazard of a patient developing hearing loss during* KANTREX *therapy?*

a In well hydrated patients with normal kidney function receiving KANTREX at the recommended dosage schedule, the hazard of ototoxic reactions is negligible. In patients with impaired kidney function, the risk of ototoxic reactions is sharply increased, and in such cases the dosage should be reduced. Finegold has stated: "Toxicity inherent in the drug can be avoided or minimized with careful management."[12]

Q *Why should renal impairment influence the dosage?*

a Because renal impairment delays the excretion of KANTREX Injection and causes an excessive accumulation in blood and tissues. Such excessive concentrations increase the risk of ototoxicity. Dosage recommendations emphasize that adequate serum levels can be achieved in such patients with a fraction of the dose suggested for patients with normal kidney function.

Q *Have you had any reports of blood dyscrasias?*

a None whatever.

Q *You mean, then, that a physician who uses* KANTREX *Injection judiciously should find it not only effective but also well tolerated?*

a Effective? Certainly, against almost all staph or "gram-negatives," even though they may be resistant to other antibiotics. Well tolerated? Yes, when given in recommended dosage. The physician can well agree with Yow, that while KANTREX Injection should not be used in mild or self-limited infections, "it should not be withheld in moderately severe or severe infections."[1] That, indeed, is the time to give it—first!

KANTREX® CAPSULES

for local gastrointestinal therapy...
not for systemic infections

Q *If* KANTREX *is not absorbed from the G.I. tract, what are the capsules used for?*

a Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *What types of intestinal infections, for instance?*

a Acute and chronic shigellosis,[14] acute and chronic salmonellosis,[4,14,15,16] amebiasis,[17] bacillary dysentery,[18] infantile diarrhea,[16,18] gastroenteritis,[19] and staphylococcal enterocolitis.[2]

Q *For preoperative bowel sterilization, why should I switch from neomycin to* KANTREX *Capsules?*

a Because KANTREX has been rated superior to neomycin for this purpose.[20,21,22] Out of 30 intestinal antiseptics studied, KANTREX was designated "the only single agent classified as a preferred drug."[21] KANTREX "consistently eliminated all aerobic bacteria within 72 hours (and often within 24 to 36 hours) if a purgative was given with the first dose to expedite passage through the gastrointestinal tract."[12]

Q *Is that all the advantage* KANTREX *has over neomycin for preoperative bowel sterilization?*

a Not at all, there are several others. Diarrhea, nausea and vomiting have not been observed with KANTREX, though they occur frequently with neomycin; yeasts do not proliferate, in contrast to rapid growth with neomycin; and clostridia are well controlled with KANTREX, and not controlled with neomycin.[20,21,22]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis; staph enteritis and gastroenteritis.

DOSAGE: INTRAMUSCULAR ROUTE

Usual daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses. (See detailed recommendations in insert accompanying each package.)

TOXICITY

When dosage recommendations are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of severe ototoxic reactions is negligible.

In patients with impaired renal function or pre-renal azotemia, the daily dose of KANTREX should be reduced to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 5 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

REFERENCES:

1. Yow, E. M.: Antibiotic Therapy for Staphylococcal Diseases. H. Welch and M. Finland, eds., Medical Encyclopedia. New York, 1959, p. 167. 2. Yow, E. M.: Practitioner 182:759, 1959. 3. Davies, F. G.: Ann. N. Y. Acad. Sci. 76:129, 1958. 4. Finegold, S. M., et al.: *Ibid.* 76:319, 1958. 5. Finegold, S. M., et al.: Antibiotics Annual 1958-9, p. 606. 6. Greey, P. H., and Wightman, K. J. R.: Annals N. Y. Acad. Sci. 76:224, 1958. 7. Huang, A. A., Sarria, A., and High, R. H.: Antibiotics Annual 1958-9, p. 687. 8. Yow, E. M., and Monzon, O. T.: Annals N. Y. Acad. Sci. 76:372, 1958. 9. Griffith, L. J., and Ostrander, W. E.: Ant. & Chemo. 9:416, 1959. 10. Leming, B. H., Jr.: Personal communication. 11. Lattimer, J. K., et al.: J.A.M.A. 170:938, 1959. 12. Finegold, S. M.: A.M.A. Arch. Int. Med. 104:15, 1959. 13. Rutenburg, A. M., et al.: Ann. N. Y. Acad. Sci. 76:348, 1958. 14. Thurman, W. G., and Platou, R. V.: *Ibid.* 76:230, 1958. 15. Yow, E. M., and Monzon, O. T.: Antibiotics Annual 1958-9, p. 736. 16. Thurman, W. G., and Platou, R. V.: Antibiotics Annual 1958-9, p. 806. 17. Ruiz Sanchez, F., et al.: *Ibid.*, p. 725. 18. Fujii, R., et al.: World-wide Abst. Gen. Med. 2:28, 1959. 19. High, R. H., Sarria, A., and Huang, N. N.: Ann. N. Y. Acad. Sci. 76:289, 1958. 20. Cohn, I., Jr.: *Ibid.* 76:212, 1958. 21. Cohn, I., Jr., and Longacre, A. B.: Antibiotics Annual 1958-9, p. 761. 22. Cohn, I., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959.

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new Noludar 300

300 mg CAPSULES

A good night's sleep can be described in many ways, but "natural" comes closest to the kind of sound, refreshing sleep your patients will enjoy when you prescribe new NOLUDAR 300. Prompt action ... unsurpassed safety ... 6 to 8 hours of undisturbed rest ... and a cheerful awakening without "hangover"—such is the quality of sleep with NOLUDAR. *Well tolerated, non-barbiturate, non-addictive, virtually free of even minor side reactions.* DOSAGE: Adults—One 300-mg capsule before retiring. Also available in 200-mg tablets for gentle hypnotic effect and 50-mg for daytime sedation.

NOLUDAR®—brand of methyprylon

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NEW PRODUCT

a steady vitamin stream all day long...

not a vitamin flash flood

'Fortespan' does not release a flood of vitamins that is quickly dissipated by destruction and excretion. Instead, your patient receives a steady stream of vitamins all day long after one 'Fortespan' capsule in the morning. This new method of presenting therapeutic multivitamins is designed to provide more efficient utilization and less vitamin waste by slowly releasing a continuous supply of the water-soluble vitamins over a prolonged period. Each capsule contains the following water-soluble vitamins in sustained release form: thiamine mononitrate (B_1), 6 mg.; riboflavin (B_2 as the phosphate), 6 mg.; pyridoxine HCl (B_6), 6 mg.; Vitamin B_{12}, 6 mcg.; nicotinamide, 60 mg.; pantothenic acid (as *dl*-panthenol), 6 mg.; and ascorbic acid (C), 150 mg. 'Fortespan' also contains these fat-soluble vitamins (which are readily absorbed and stored and, therefore, are not in sustained release form but are present as a larger pellet in the colored end of the 'Fortespan' capsule): Vitamin A, 15,000 U.S.P. Units; and Vitamin D, 1,000 U.S.P. Units. Smith Kline & French Laboratories, Philadelphia.

Fortespan*

brand of high potency multivitamins—therapeutic formula—in Spansule® sustained release capsules

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PREMENSTRUAL TENSION

"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients with these complaints were completely relieved."

"Where tension, nervousness, and headaches are major factors, chlorothiazide may provide relief; approximately half of the patients in this series [of 50] were benefited . . ."

Jungck, E.C., Barfield, W. and Greenblatt, R.B.: J.A.M.A. 169:112, (Jan. 10) 1959.

Dosage: One or two 500 mg. tablets DIURIL daily—beginning the first morning of symptoms and continuing until after onset of menses.

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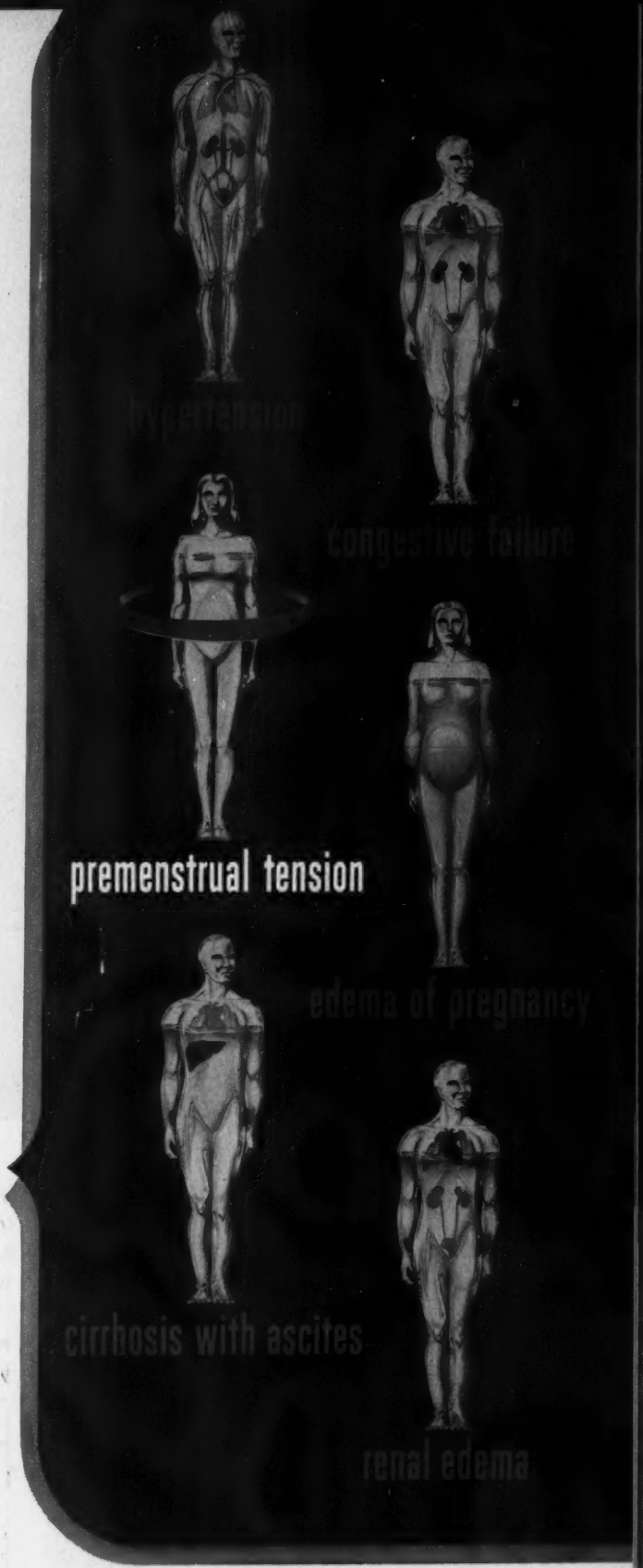
CHLOROTHIAZIDE

a continuing and consistently outstanding record of safety and efficacy in:



Supplied: 250 mg. and 500 mg. scored tablets DIURIL (Chlorothiazide). DIURIL is a trademark of Merck & Co., Inc. Additional information is available to the physician on request.

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Late evening dose doesn't interfere with sleep.

Since Tenuate is free of CNS stimulation, it can be given in mid-evening, when TV snacks run up a high calorie count. Doses given to control evening snacks will not interfere with sleep.[3]

Tenuate cuts the urge to eat. So well, in fact, that weight loss on Tenuate averages over 1.5 lbs. a week. (see chart)

Safe—Tenuate can be used even in overweight cardiacs or hypertensives.

EKG studies substantiate Tenuate's lack of appreciable CNS stimulation. No effect on heart rate, blood pressure, pulse or respiration is demonstrable.[3] Thus Tenuate is particularly well suited for hypertensive and cardiac patients — those whose weight *must* come down.

PROOF OF WEIGHT LOSS[2-4]

In a series of 102 patients, the following weight losses were obtained:

Lbs./Week	Number of Patients	% Patients
0.1-0.9	23	22.54
1.0-1.9	51	50.00
2.0-2.9	25	24.52
3.0-4.0	3	2.94
	102 PATIENTS	100%

new

TENUATE

(diethylpropion)

hunger control with no CNS stimulation[1-7]

Indications: The overweight patient, including adolescent, geriatric and gravid, as well as special risk situations – cardiac, hypertensive, diabetic.

Dosage: One 25 mg. tablet one hour before meals. To control nighttime hunger, an additional tablet taken in mid-evening will not induce insomnia.

References: 1. Huels, G.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959. 2. Horwitz, S.: *personal communication.* 3. Spielman, A. D.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959. 4. Ravetz, E.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959. 5. Decina, L. J.: Exper. Med. & Surg. *in press.* 6. Scanlan, J. S.: *in press.* 7. Kroetz and Storck: *personal communication.* 8. Alfaro, R. D.; Gracanin, V., and Schleuter, E.: *to be published.*

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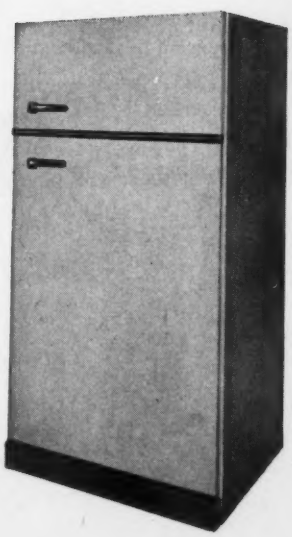


thwarts refrigerator raiders

TENUATE

Especially for late evening snackers. Controls hunger without producing sleeplessness.

selective peripheral action to relieve symptoms of arterial insufficiency[1]—

intermittent claudication
leg pain
coldness and numbness of extremities
in
Arteriosclerosis Obliterans
Diabetic Vascular Disease
Buerger's Disease
Thrombophlebitis

NEW VASODILAN®

Pronounced VĀ-ZŌ-DY-LAN

Isoxsuprine hydrochloride, Mead Johnson

a myo- -vascular relaxant

brings blood to the deep tissues by direct action on the arterial wall[1-3]

with remarkable safety in recommended doses[1-7]
without adverse effects on coronary flow[1, 2]
without troublesome hypotension or tachycardia[1, 2]
without renal effects[1, 2]
without increase in gastric acidity[2]
without ganglionic blocking action[1-3]
without development of tolerance[1]

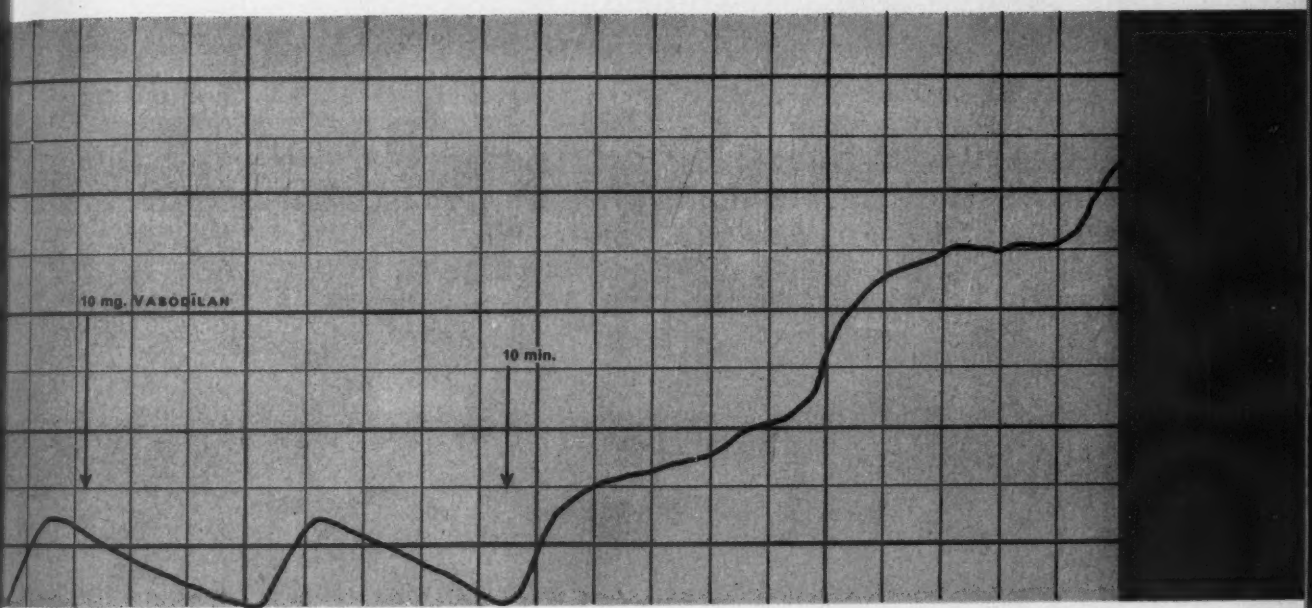
76859

Availability: VASODILAN Tablets, 10 mg., bottles of 100. VASODILAN Injection, Ampuls, 2 cc. (5 mg./cc.), boxes of 6.

Oral Dosage: 10 or 20 mg. (1 or 2 tablets) three or four times a day. For complete details on indications, dosage, administration and clinical background of VASODILAN, see the brochure on this product available on request from Mead Johnson and Company, Evansville 21, Indiana.

References: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (August) 1959. (2) Kaindl, F.; Pärtan, J., and Polsterer, P.: Wien. klin. Wchnschr. *68*:186, 1956. (3) Brücke, F., et al.: Wien. klin. Wchnschr. *68*:183, 1956. (4) Nash, C. B.; Drinnon, V., and Clark, B. B.; abstracted, Fed. Proc. *17*:397 (March) 1958. (5) Singer, R.: Wien. med. Wchnschr. *107*:734-736 (Sept.) 1957. (6) Dungan, K. W., and Lish, P. M.; abstracted, Fed. Proc. *17*:365 (March) 1958. (7) Billiottet, J., and Ferrand, J.: Semaine méd. *34*:635-637 (May) 1958.

Plethysmographic tracing of toe showing increase in blood flow starting 10 minutes after injection of 10 mg. of VASODILAN. Increased flow maintained for one hour. (Plethysmographic basic line already established.) *Courtesy S. S. Samuels, M. D., New York*



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Rynatan® Expectorant keeps heads and chests crystal clear

all day or night with 1 oral dose and with a remarkable

lack of drowsiness or any other side effect

The only long-acting non-narcotic, anti-tussive expectorant available, Rynatan Expectorant controls cough and bronchospasm, promotes expectoration . . . at the same time relieves upper and lower respiratory tract congestion . . . clears all air passages. And the Durabond Principle—a Neisler exclusive—assures smooth and sustained therapeutic action for hours with few if any side effects, because drug absorption is independent of intestinal motility, pH or other physiologic factors. The sympathomimetic amines present in the formulation also help offset any drowsiness from the antihistamine or sedative ingredients. Each 5 cc. of caramel-flavored suspension contains: carbetapentane tannate (non-narcotic) 30 mg.; ephedrine tannate, 5.0 mg.; phenylephrine tannate, 5.0 mg.; chlorpheniramine tannate, 2.0 mg.; and pyrilamine tannate, 12.5 mg. IRWIN, NEISLER & CO. · DECATUR, ILLINOIS

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a logical combination in appetite control

BAMADEX®

meprobamate with dextro-amphetamine sulfate LEDERLE

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meprobamate eases tensions of dieting

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d-amphetamine depresses appetite and elevates mood

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...without overstimulation

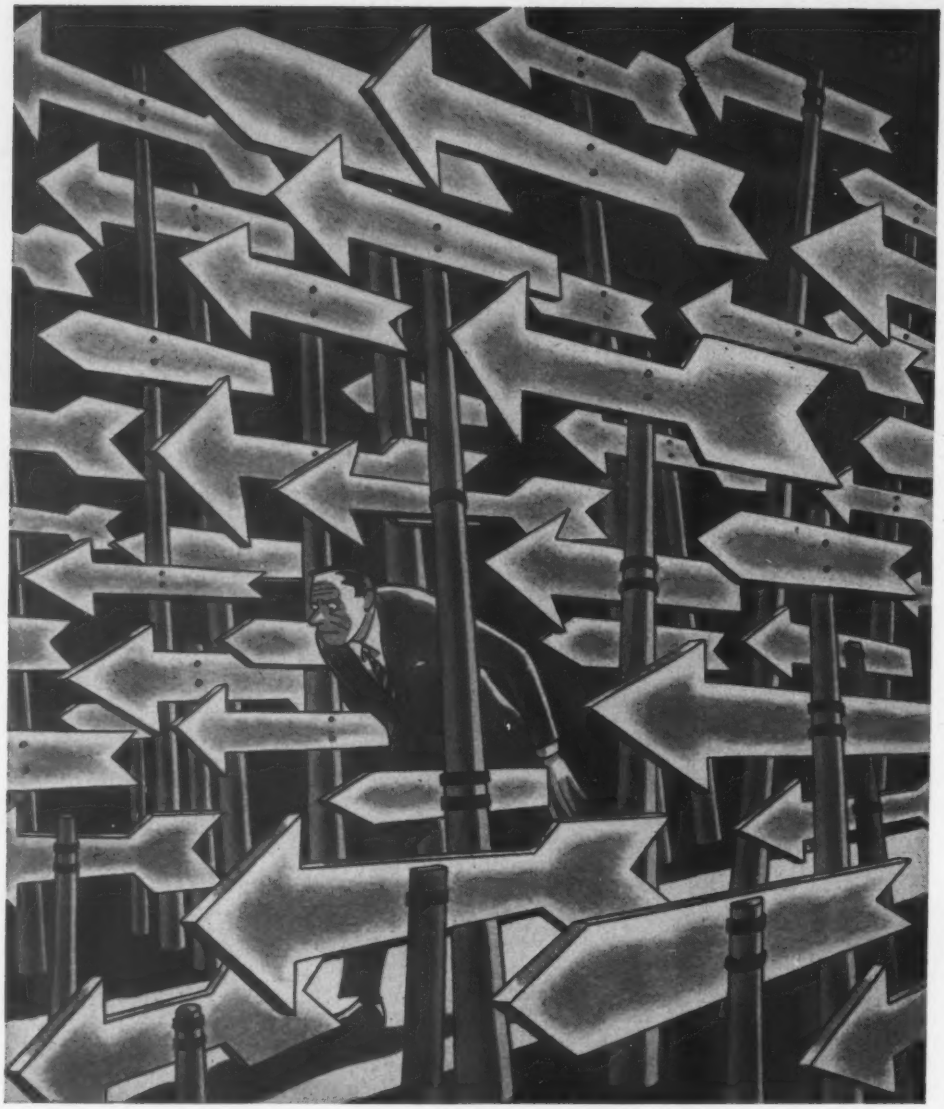
...without insomnia

...without barbiturate hangover

Each coated tablet (pink) contains:
d-amphetamine sulfate .... 5 mg.
meprobamate ..... 400 mg.
Dosage: One tablet taken one-half to one hour before each meal.

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



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Many diabetics on insulin live highly restricted lives. They may not miss or delay a meal; they must neither over-work nor under-exercise for fear of complications.

For 3 out of 4 of these patients, Orinase* offers better control and an easier, more normal life. Because Orinase controls diabetes effectively and *smoothly* in responsive patients, they can enjoy a new freedom. And some diabetics, who cannot be managed on Orinase alone, do best on *combined* Orinase-insulin therapy.

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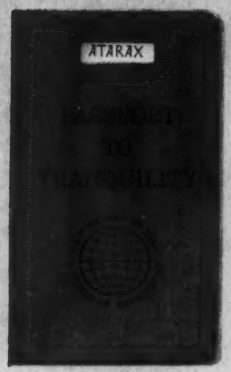
A GUIDE TO

THE REALMS OF THERAPY BEST ATTAINED WITH



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(brand of hydroxyzine)

World-wide record of effectiveness—over 200 laboratory and clinical papers from 14 countries.
Widest latitude of safety and flexibility—no serious adverse clinical reaction ever documented.
Chemically distinct among tranquilizers—not a phenothiazine or a meprobamate.
Added frontiers of usefulness—antihistaminic; mildly antiarrhythmic; does not stimulate gastric secretion.

Special Advantages	Supportive Clinical Observation	...and for additional evidence
IN CHILDREN unusually safe; tasty syrup, 10 mg. tablet	"...Atarax appeared to reduce anxiety and restlessness, improve sleep patterns and make the child more amenable to the development of new patterns of behavior...." Freedman, A. M.: Pediat. Clin. North America 5:573 (Aug.) 1958.	Bayart, J.: Acta paediat. belg. 10:164, 1956. Ayd, F. J., Jr.: California Med. 87:75 (Aug.) 1957. Nathan, L. A., and Andelman, M. B.: Illinois M. J. 112:171 (Oct.) 1957.
IN ELDERLY PATIENTS well tolerated by debilitated patients	"...seems to be the agent of choice in patients suffering from removal disorientation, confusion, conversion hysteria and other psychoneurotic conditions occurring in old age." Smigel, J. O., et al.: J. Am. Geriatrics Soc. 7:61 (Jan.) 1959.	Settel, E.: Am. Pract. & Digest Treat. 8:1584 (Oct.) 1957. Negri, F.: Minerva med. 48:607 (Feb. 21) 1957. Shalowitz, M.: Geriatrics 11:312 (July) 1956.
IN ALLERGIC PATIENTS useful adjunctive therapy for asthma and dermatosis; particularly effective in urticaria	"All [asthmatic] patients reported greater calmness and were able to rest and sleep better...and led a more normal life....In chronic and acute urticaria, however, hydroxyzine was effective as the sole medicament." Santos, I. M., and Unger, L.: Presented at 14th Annual Congress, American College of Allergists, Atlantic City, New Jersey, April 23-25, 1958.	Eisenberg, B. C.: J.A.M.A. 169:14 (Jan. 3) 1959. Coirault, R., et al.: Presse méd. 64:2239 (Dec. 26) 1956. Robinson, H. M., Jr., et al.: South. M. J. 50:1282 (Oct.) 1957.
IN HYPEREMOTIVE ADULTS does not impair mental acuity	"...especially well-suited for ambulatory neurotics who must work, drive a car, or operate machinery." Ayd, F. J., Jr.: New York J. Med. 57:1742 (May 15) 1957.	Garber, R. C., Jr.: J. Florida M. A. 45:549 (Nov.) 1958. Menger, H. C.: New York J. Med. 58:1684 (May 15) 1958. Farah, L.: Internat. Rec. Med. 169:379 (June) 1956.

SUPPLIED: Tablets, 10 mg., 25 mg., 100 mg.; bottles of 100. Syrup (10 mg. per tsp.), pint bottles. Parenteral Solution: 25 mg./cc. in 10 cc. multiple-dose vials; 50 mg./cc. in 2 cc. ampules.

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Toes are to wiggle

A lap is so you don't get crumbs on the floor

Rugs are so dogs have napkins

REDISOL® is so kids have better appetites

Redisol (Cyanocobalamin, crystalline vitamin B_{12}) often stimulates children's appetites with consequent weight gain.
Tiny **Redisol Tablets** (25, 50, 100, 250 mcg.) dissolve instantly in the mouth, on food or in liquids.
Also available: cherry-flavored **Redisol Elixir** (5 mcg. per 5-cc. teaspoonful); **Redisol Injectable,**
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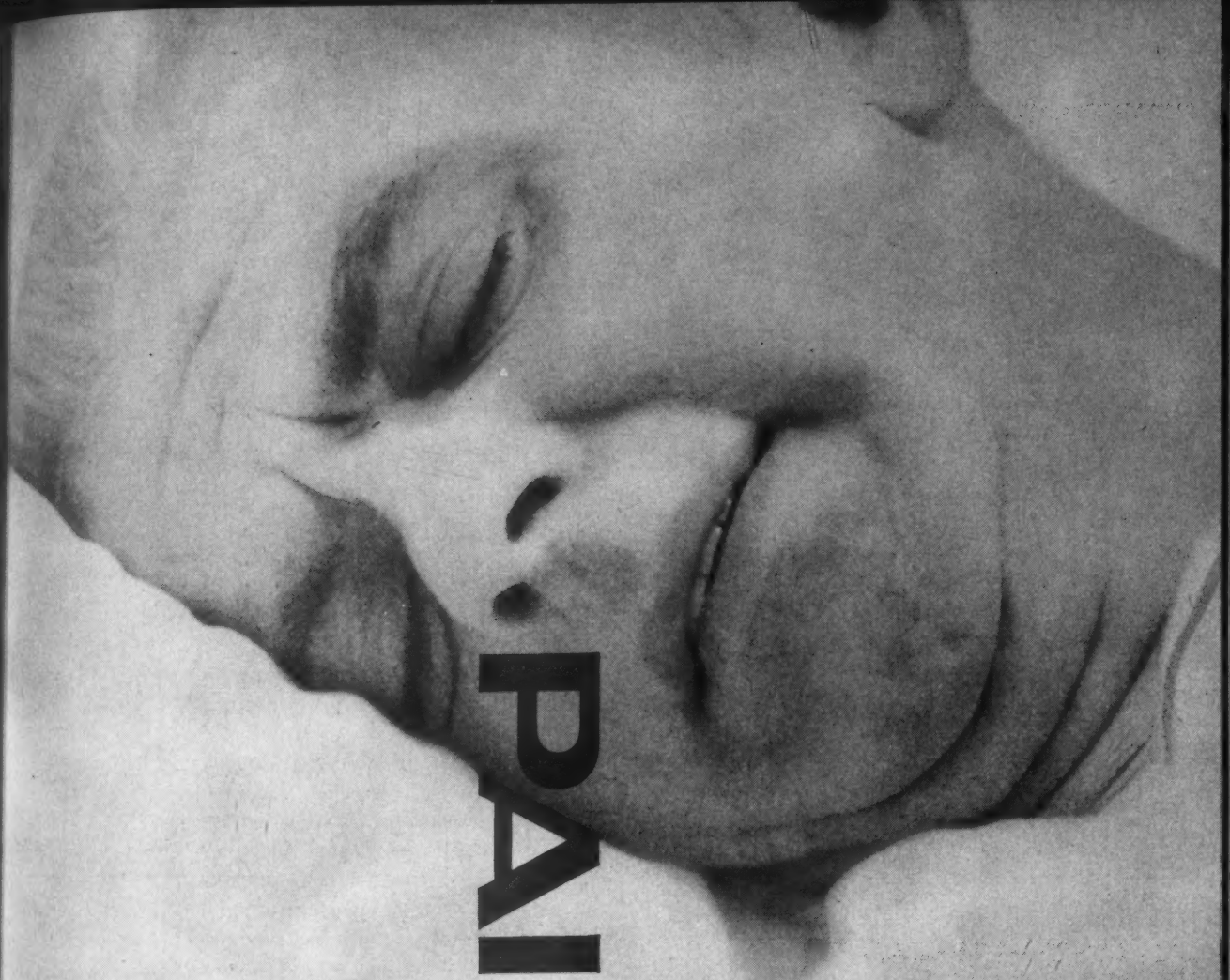

PAIN

Zactirin®

Ethoheptazine Citrate (75 mg.) with Acetylsalicylic Acid (325 mg.), Wyeth

Relief for the pain problems of grippe

and other upper respiratory infections

Myalgia • Arthralgia • Pleurisy • Severe headache • Retro-orbital discomfort

Consider ZACTIRIN when effective analgesia is required to cope with stubborn pain symptoms of upper respiratory infections. ZACTIRIN aids these patients by both easing pain and combating inflammation. Non-narcotic and well tolerated, ZACTIRIN gives pain relief equivalent to that of codeine. *Supplied: Tablets, bottles of 48.*

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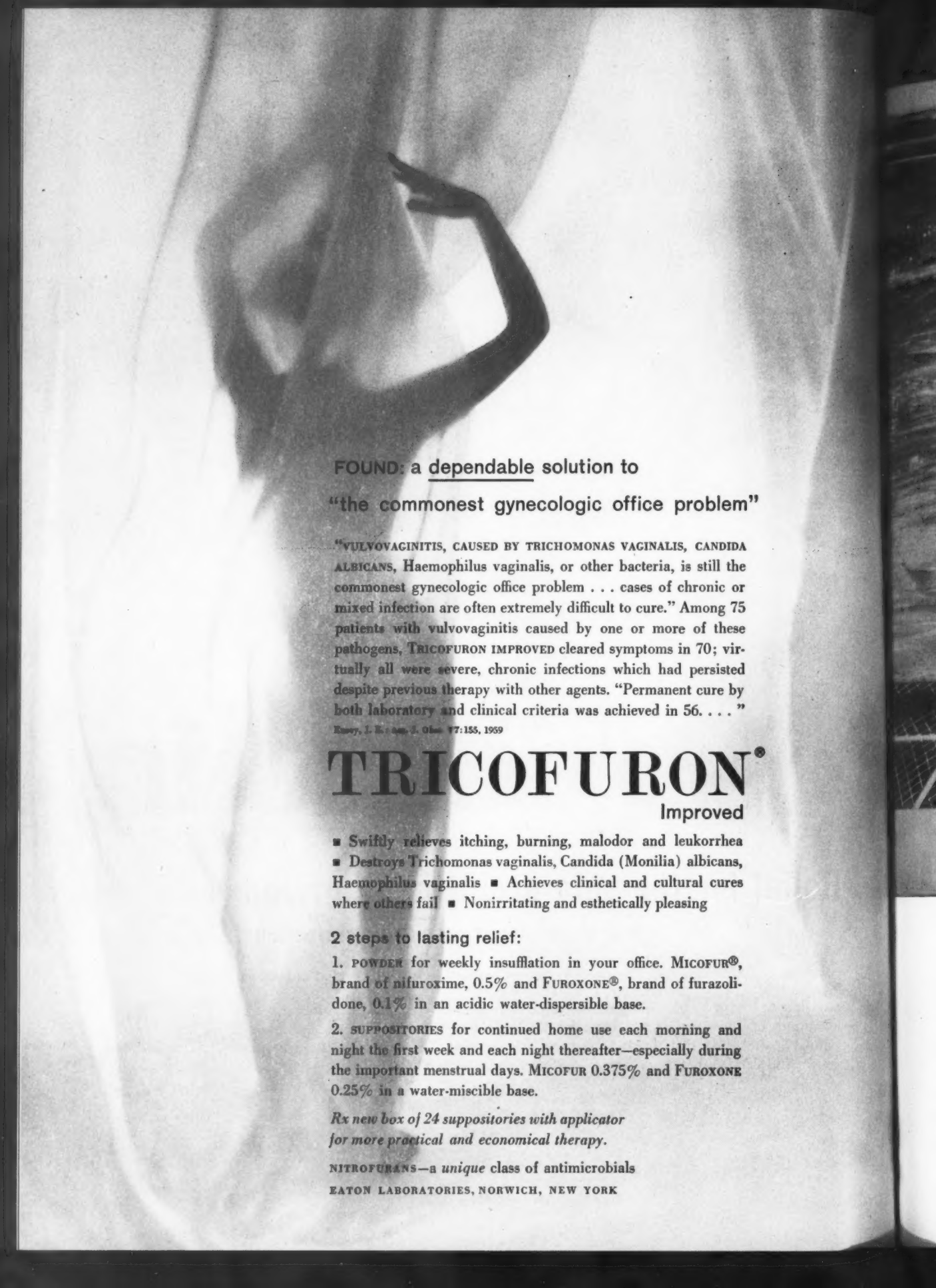
A Century of Service to Medicine



FOUND: a dependable solution to "the commonest gynecologic office problem"

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . . "

Emery, J. R.: Am. J. Obst. 77:155, 1959

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Improved

■ Swiftly relieves itching, burning, malodor and leukorrhea ■ Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing

2 steps to lasting relief:

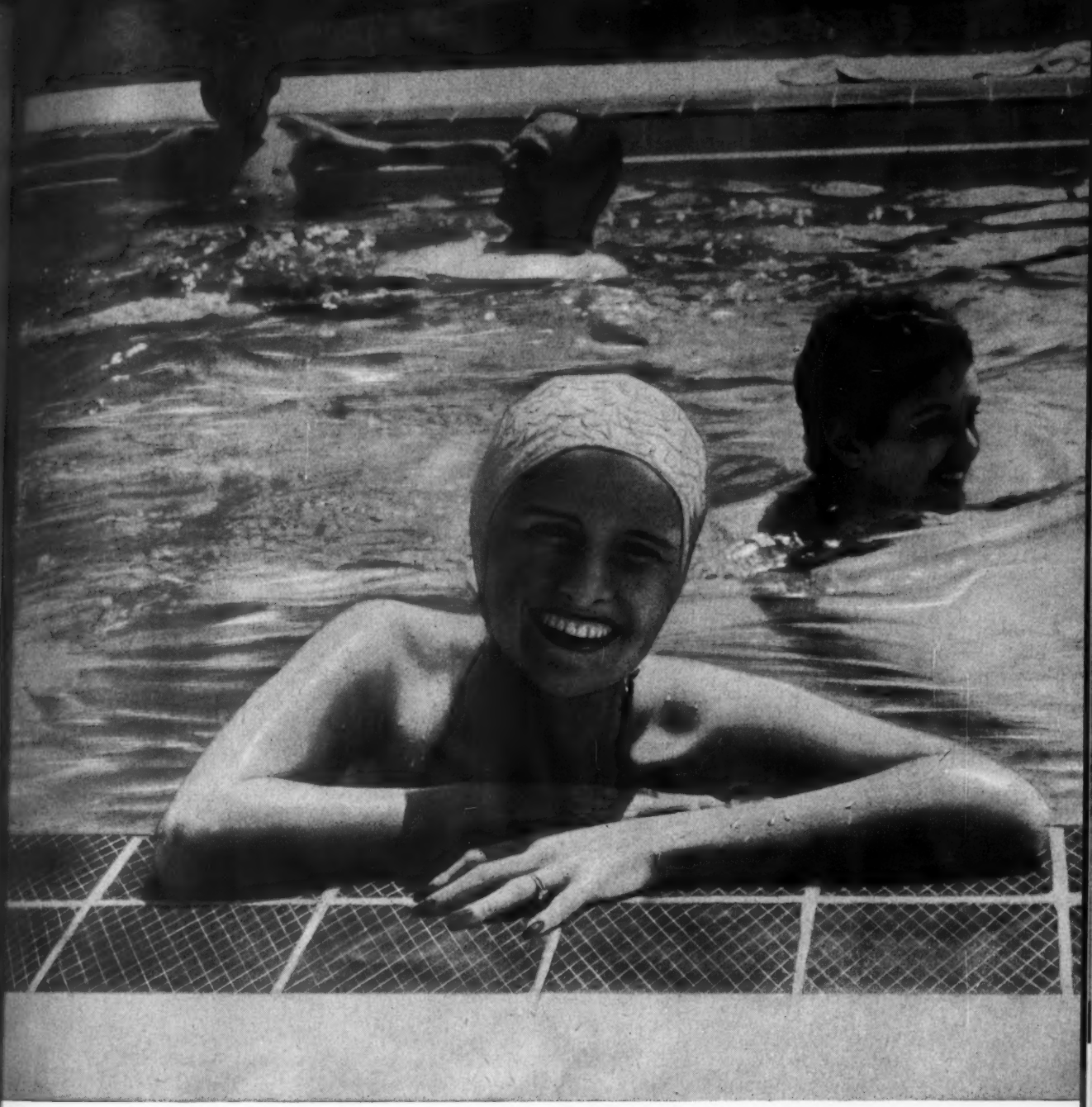
1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

NITROFURANS—a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK



Of course, women like "Premarin"®

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs nursing—"Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

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Each MYADEC Capsule contains: VITAMINS: Vitamin B_{12} crystalline—5 mcg.; Vitamin B_2 (riboflavin)—10 mg.; Vitamin B_6 (pyridoxine hydrochloride)—2 mg.; Vitamin B_1 mononitrate—10 mg.; Nicotinamide (niacinamide)—100 mg.; Vitamin C (ascorbic acid)—150 mg.; Vitamin A—25,000 units; Vitamin D—1,000 units; Vitamin E (mixed tocopheryl acetates)—5 I.U.; MINERALS (as inorganic salts): Iodine—0.15 mg.; Manganese—1.0 mg.; Cobalt—0.1 mg.; Potassium—5.0 mg.; Molybdenum—0.2 mg.; Iron—15.0 mg.; Copper—1.0 mg.; Zinc—1.5 mg.; Magnesium—6.0 mg.; Calcium—105.0 mg.; Phosphorus—80.0 mg. Bottles of 30, 100, 250, and 1,000.

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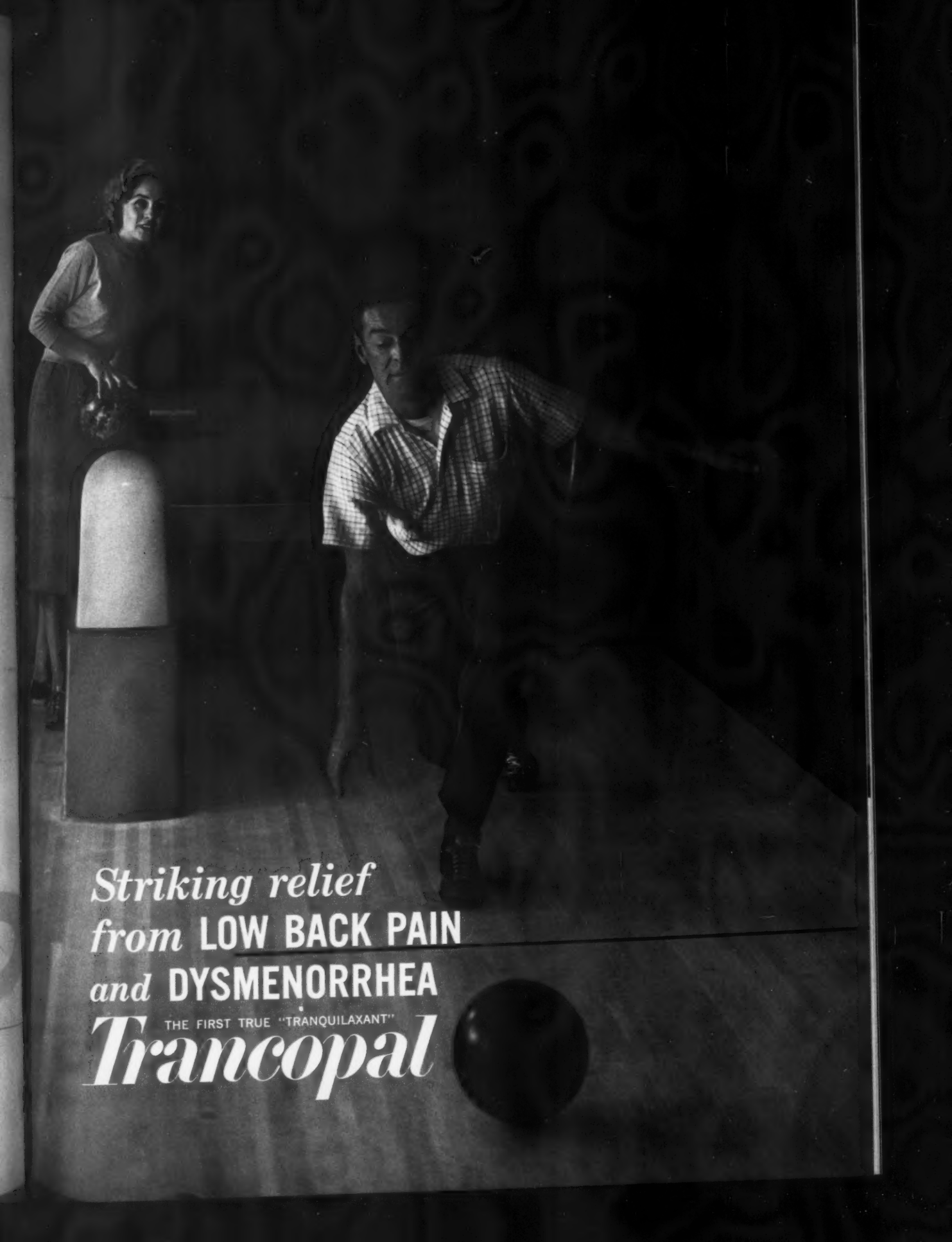
Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is what you can expect when you prescribe

for dysmenorrhea

and premenstrual tension

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain

Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:		Psychogenic:
Low back pain (lumbago, etc.)	Fibrositis	Anxiety and tension states
Neck pain (torticollis)	Ankle sprain, tennis elbow	Dysmenorrhea
Bursitis	Myositis	Premenstrual tension
Rheumatoid arthritis	Postoperative muscle spasm	Asthma
Osteoarthritis		Angina pectoris
Disc syndrome		Alcoholism

Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH ▶

Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

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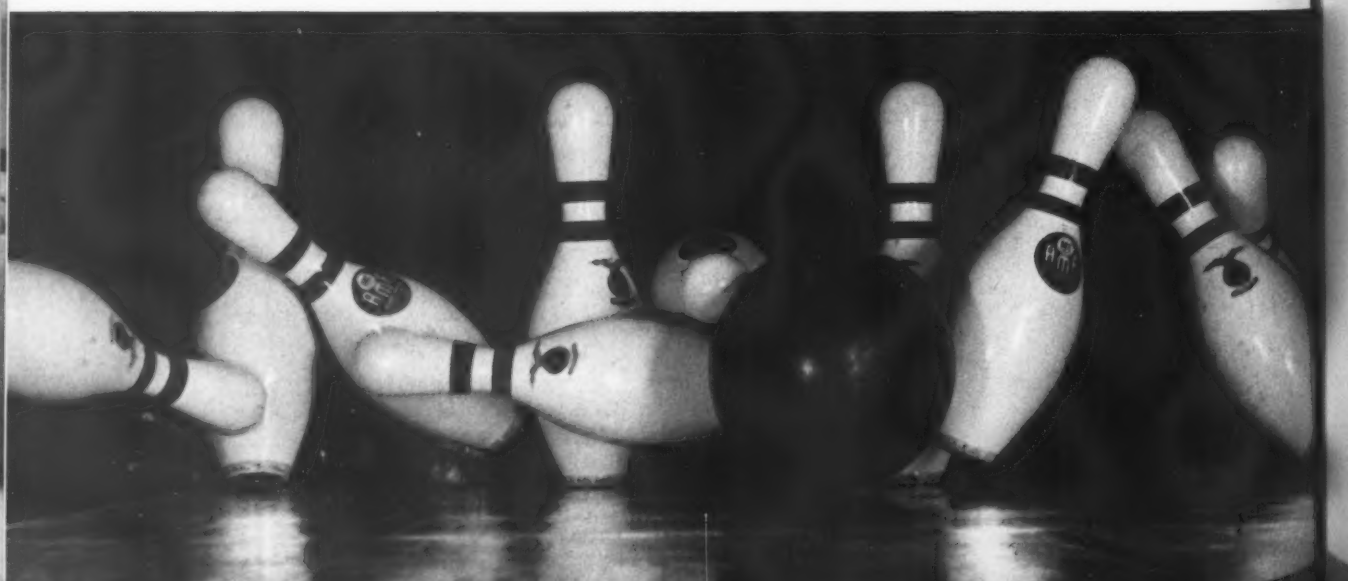

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"... an efficient and convenient means of dealing with the problem of acute agitation in alcoholic intoxication ... important was the absence of noticeable respiratory depression...."

Miller, R. F.: Clin. Rev, 1:10 (July) 1958

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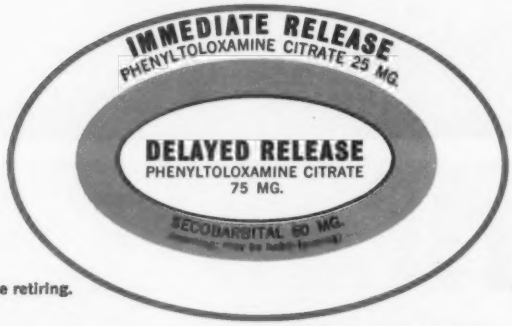
Sleep comes quick, sure and sound, with new Hyptran. The outer layer contains an immediate calming dosage of phenyltoloxamine, a mild, certain non-phenothiazine tranquilizer to support short-acting secobarbital. This fast-acting, quickly metabolized barbiturate acts directly on the higher cerebral levels and quickly brings needed sleep. Hyptran's inner core of phenyltoloxamine, released later in the night, controls insomnia-causing anxieties, keeps them from "breaking through" and interrupting sleep. Patients awake calm and clear-headed, fully refreshed mentally and physically.



DOSAGE: 1-2 tablets before retiring.

SUPPLIED: Bottles of 100.

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throughout the day—with a negligible incidence of restlessness and insomnia.

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The *low cost* antibacterial prescription
with assured *safety* and *effectiveness*

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safe • effective • economical

"...its simplicity of administration, safety, clinical response and reasonable cost make... [Madribon] a desirable drug in instances where it is equally effective [as the antibiotics] and a choice drug in many antibiotic-resistant cases."[1]

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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

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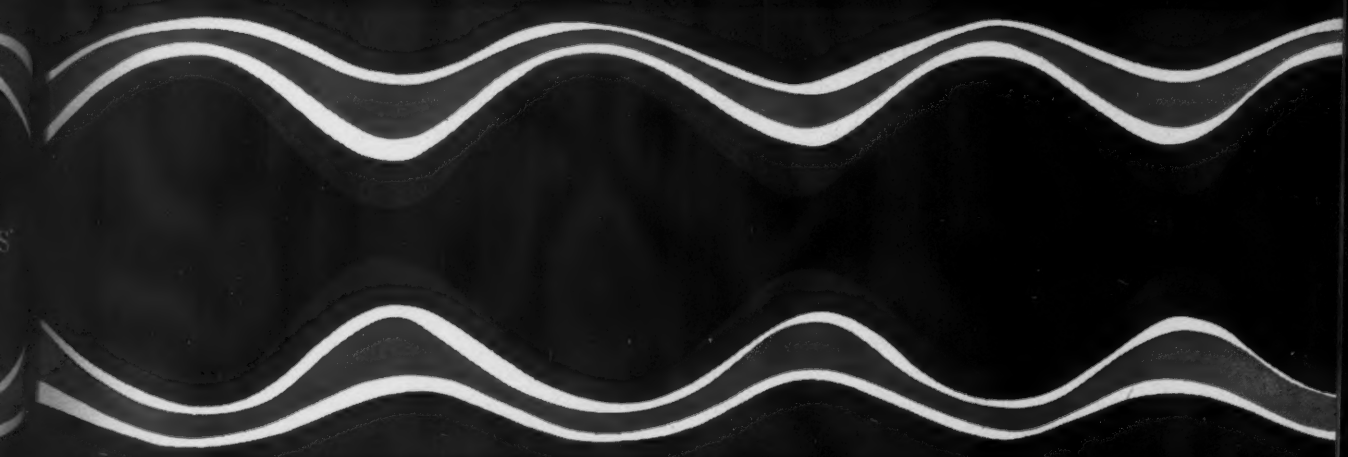

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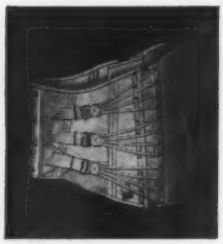

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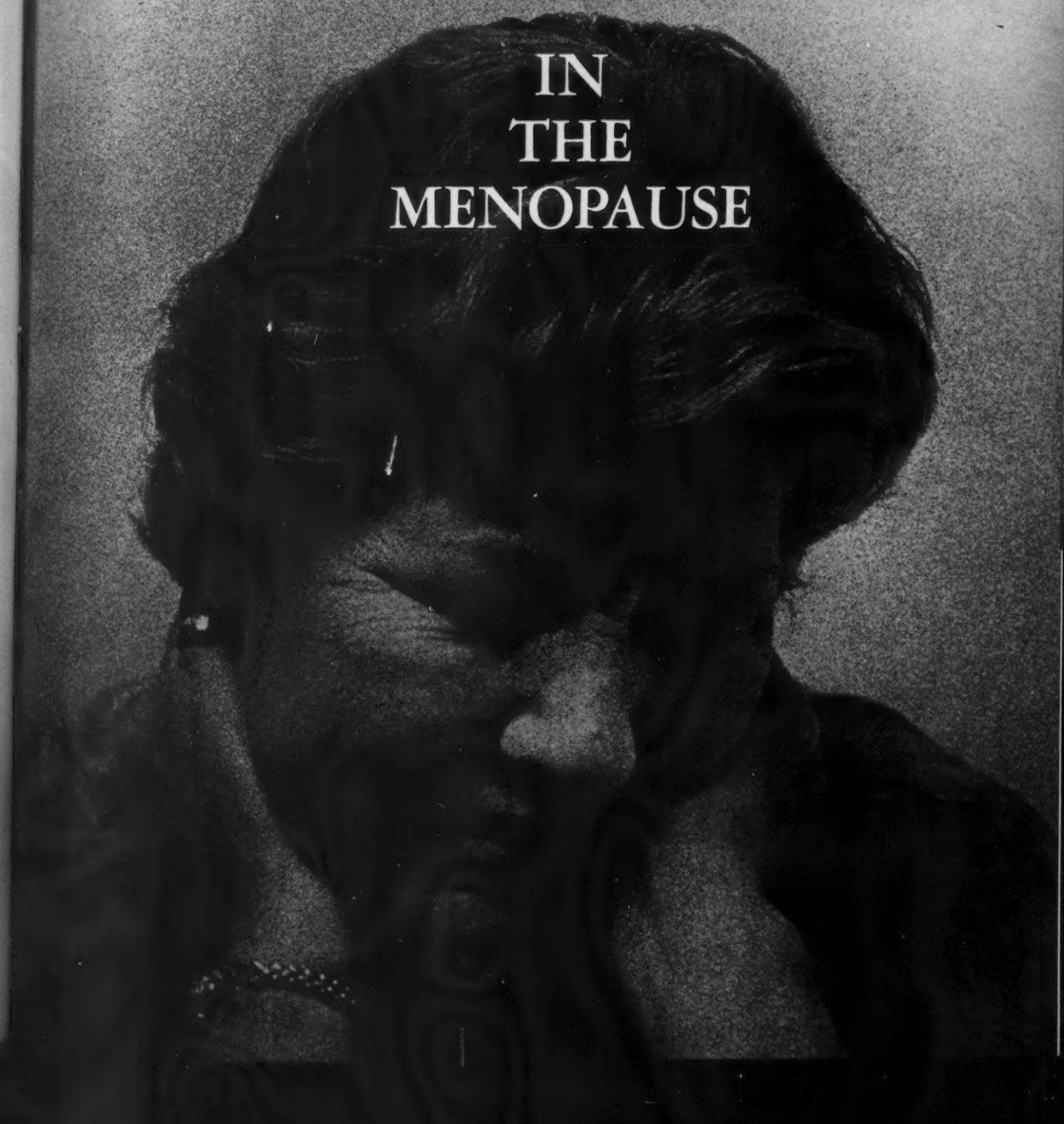

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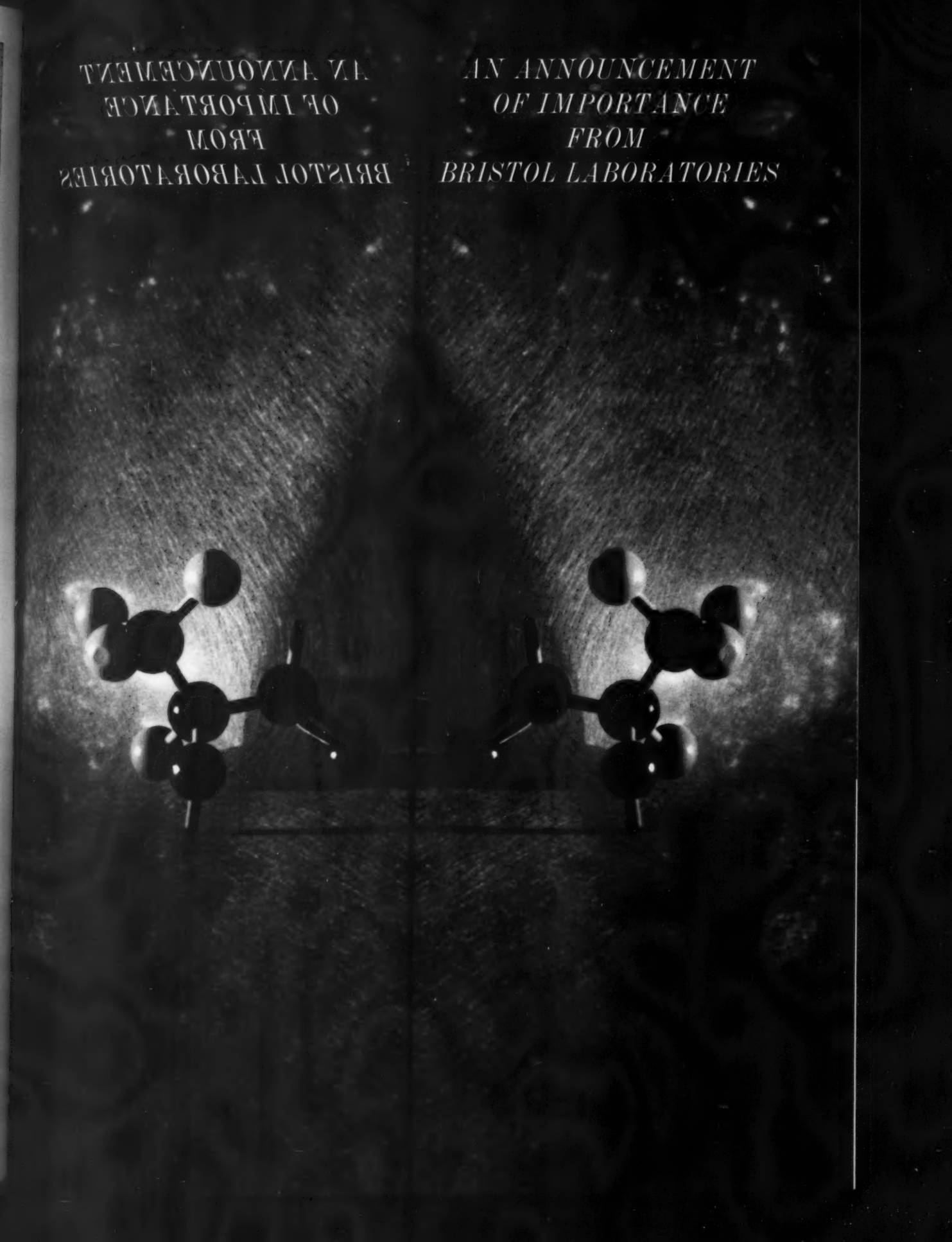
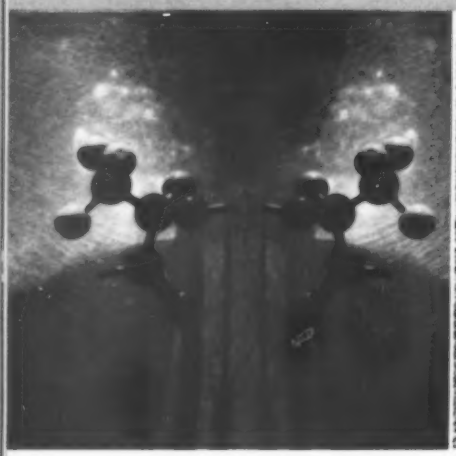
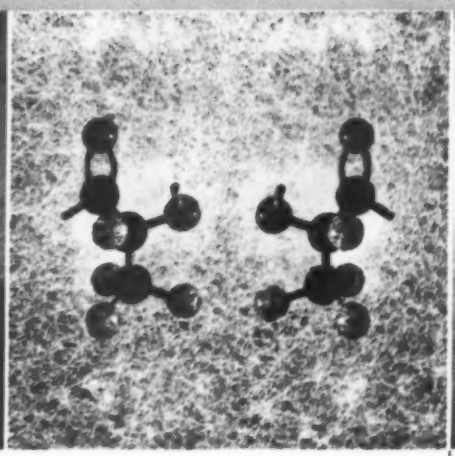


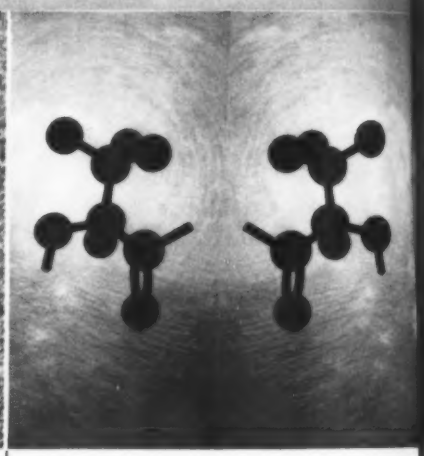
The first synthetic penicillin available for general clinical use

MAJOR THERAPEUTIC *AD*

SYNC







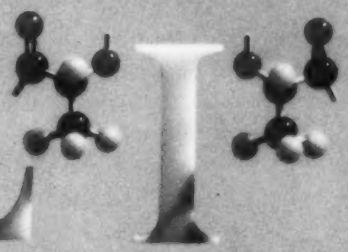
BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V

SAFER ORAL ROUTE PROVIDES HIGHER BLOOD LEVELS THAN INTRAMUSCULAR PENICILLIN G

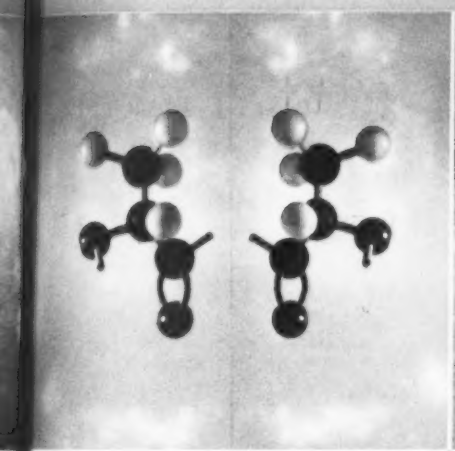
IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

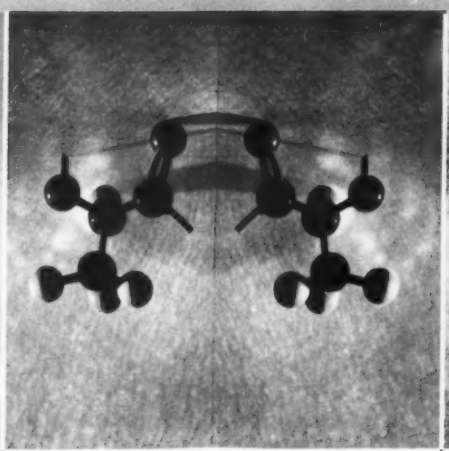
ADVANTAGES ACCOMPANY MOLECULAR ASYMMETRY

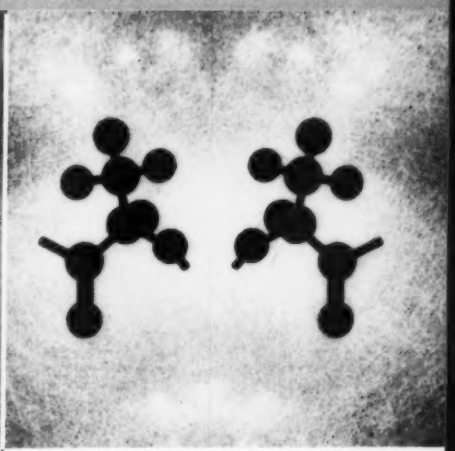
I L L I N™



POTASSIUM PENICILLIN-152







ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSE

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN

BRISTOL

ORIGIN OF A NEW SYNTHETIC PENICILLIN

In March, 1957, Dr. John C. Sheehan of the Massachusetts Institute of Technology announced the total synthesis of penicillin from common raw materials, thus solving a problem which had baffled research workers for more than 15 years. Although total synthesis was not commercially practicable, this work, sponsored by Bristol Laboratories, made possible the subsequent synthesis of new penicillins not occurring in nature. Later scientists at Beecham Laboratories in England discovered that a key intermediate (6-aminopenicillanic acid) could be produced by a fermentation process. With these achievements, large scale production of synthetic penicillins became feasible.

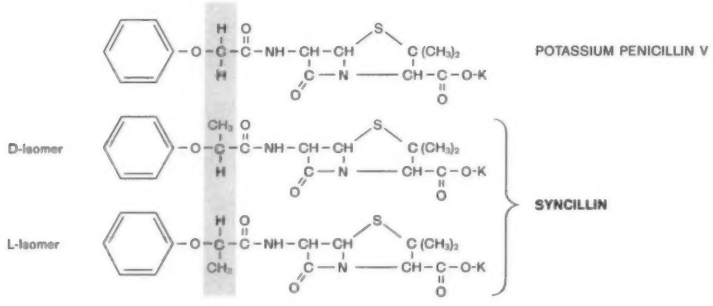
Organic chemists at Bristol then embarked upon an intensive program to develop better penicillins. Over five hundred were synthesized and underwent preliminary screening. Forty-six showed sufficient promise to warrant further investigation. Extensive microbiological, pharmacological, and clinical screening indicated that one compound, SYNCILLIN, had advantages of major importance over other penicillins.

SYNCILLIN is the N-acylation product of 6-aminopenicillanic acid and α-phenoxypropionic acid (the phenylether of lactic acid). It is freely soluble in water and remarkably resistant to decomposition by acid. The acid stability of SYNCILLIN is equivalent to that of penicillin V at pH 2 and pH 3 at 37° C.[1]

SIGNIFICANCE OF MOLECULAR ASYMMETRY AND ISOMERIC COMPLEMENTARITY

SYNCILLIN has a molecular configuration similar to penicillin V, but contains an additional CH_3 group so positioned as to render the adjacent carbon atom asymmetric. (In the formulae below, the added CH_3 group is shown in blue and the asymmetric carbon atom in red.) As a result, SYNCILLIN occurs as a mixture of two isomers.

Each isomer has been synthesized in essentially pure form and found to possess distinctive chemical and biological properties. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. As produced, SYNCILLIN is a mixture of the L-isomer and the D-isomer. As will be shown later, the antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than either isomer alone against many organisms. This phenomenon is referred to here as *isomeric complementarity*.



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

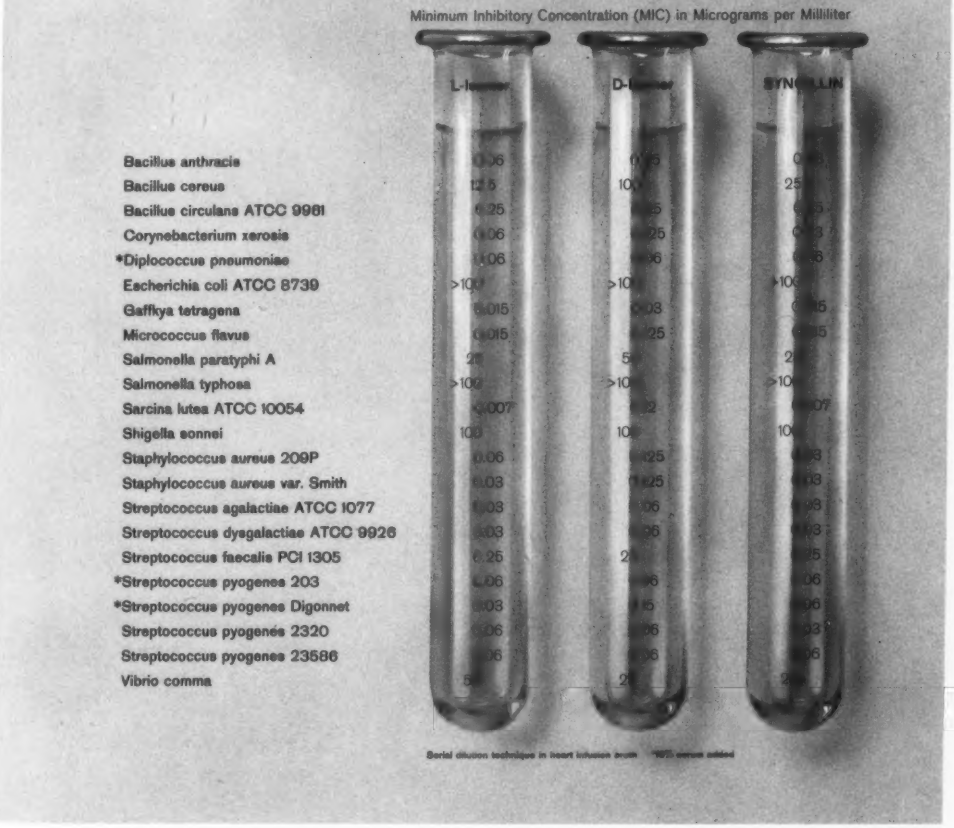
ISOMERIC COMPLEMENTARITY DEMONSTRATED IN VITRO

The *in vitro* minimum inhibitory concentration (MIC) of SYNCILLIN and of each of its two component isomers was determined for a variety of common pathogens and laboratory test organisms. As may be seen from Table 1, all three are highly effective against penicillin-susceptible staphylococci and against pneumococci, streptococci, gonococci, and corynebacteria; all are ineffective against Salmonella, *E. coli,* and other gram-negative coliform bacilli.

SYNCILLIN was more active against many of the test strains including some streptococci and staphylococci than either of its components. This demonstrates *in vitro* the phenomenon of isomeric complementarity.

TABLE 1

Minimum Concentrations of SYNCILLIN and Components Required to Inhibit a Wide Range of Bacteria



SYNCILLIN

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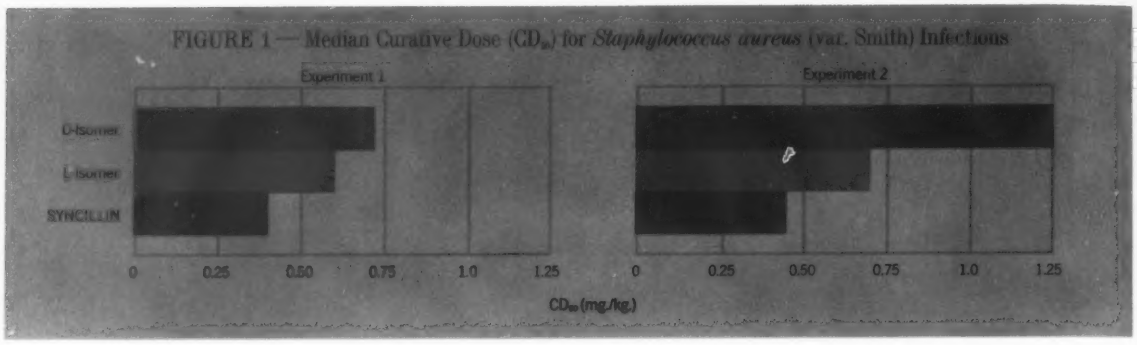
ISOMERIC COMPLEMENTARITY CONFIRMED IN VIVO

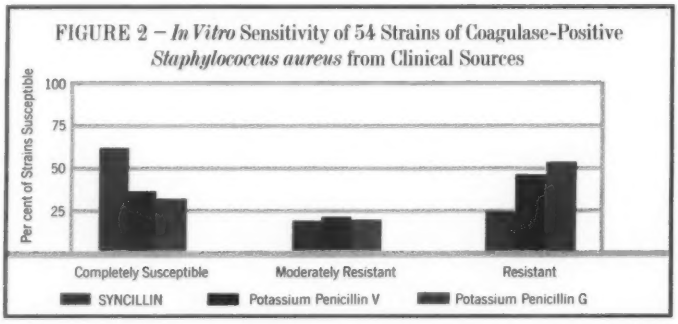
To determine the median curative dose (CD_{50}) mice were infected with 100 times the lethal dose of *Staphylococcus aureus*. Each penicillin being tested was administered intramuscularly at the same time, and the dose required to cure half the animals determined. The greater effect of the mixture of the two isomers (SYNCILLIN) is shown in two independent experiments. (See Figure 1.) Note that isomeric complementarity is thus confirmed *in vivo*.



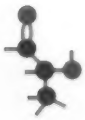
MANY STRAINS OF STAPHYLOCOCCI MORE SENSITIVE TO SYNCILLIN

SYNCILLIN has been tested against a large number of strains of *Staphylococcus aureus* isolated from clinical sources. Many organisms resistant to potassium penicillin G and potassium penicillin V proved sensitive to SYNCILLIN.

Wright[2] performed sensitivity studies on 54 strains, the majority of which were resistant or moderately resistant to penicillin V and penicillin G. Thirty-two (60%) of the strains were sensitive to SYNCILLIN, approximately twice as many as with the other penicillins. (See Figure 2.) In two-thirds of the isolates, SYNCILLIN produced inhibition at concentrations lower than those required for either of the other antibiotics. One strain was more sensitive to penicillin G.



Adapted from Wright[2]



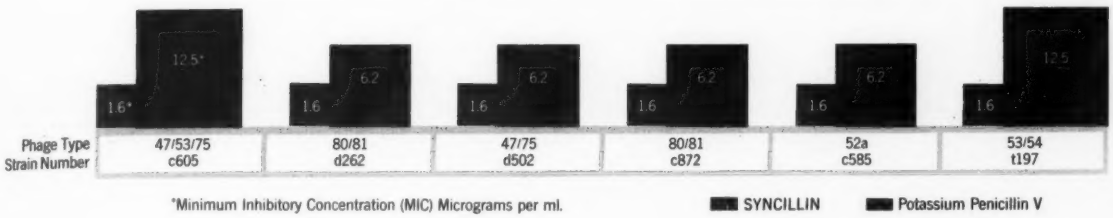
SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Of equal interest are the findings of White.[3] Six penicillin-resistant strains of staphylococci were isolated from hospital infections. None was sensitive to potassium penicillin V. All were sensitive to SYNCILLIN. (See Figure 3.)

FIGURE 3

Minimum Concentrations of SYNCILLIN Required to Inhibit
Hospital Strains of *Staphylococcus aureus* Resistant to Potassium Penicillin V

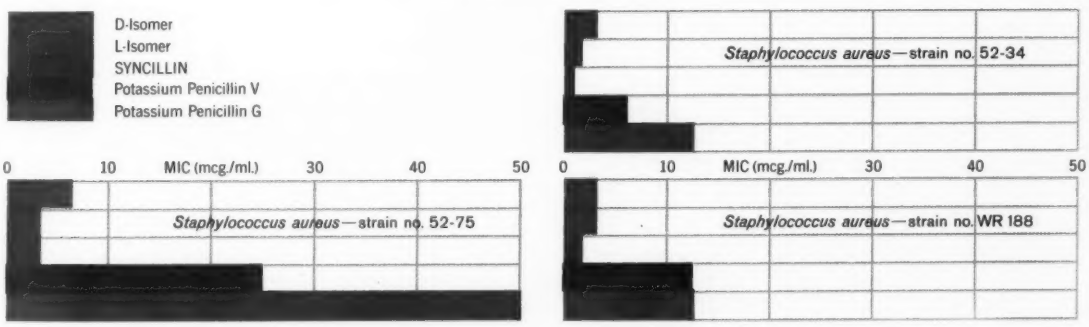


The efficacy of SYNCILLIN against the type 80/81 Staphylococcus (dangerous and widespread in hospitals) is worthy of special attention.

The complementary action of the component isomers is also seen with strains of staphylococci resistant to penicillins. Note that SYNCILLIN is more effective than either isomer against strains 52-34 and WR 188. (See Figure 4.) Against all three strains, SYNCILLIN is effective at concentrations below serum levels, while penicillins V and G are ineffective.

FIGURE 4

Minimum Inhibitory Concentrations (MIC) for Coagulase-Positive
Penicillin-Resistant Strains of *Staphylococcus aureus*



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figure 1)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

SYNCILLIN

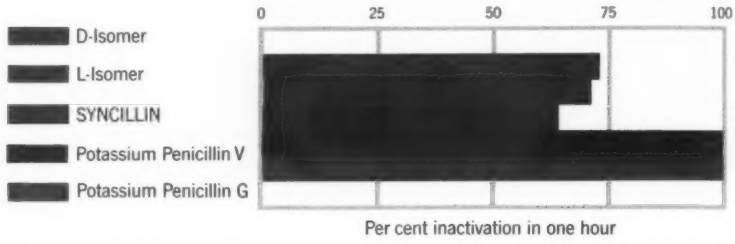
major therapeutic advantages accompany molecular asymmetry

ISOMERIC COMPLEMENTARITY SHOWN BY REDUCED RATE OF INACTIVATION BY PENICILLINASE

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms.[4] As shown in Figure 5, SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers – a further demonstration of isomeric complementarity. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V and penicillin G.

Resistance to SYNCILLIN develops in a slow, step-wise manner characteristic of other penicillins, in contrast to the usually rapid development of resistance to streptomycin.

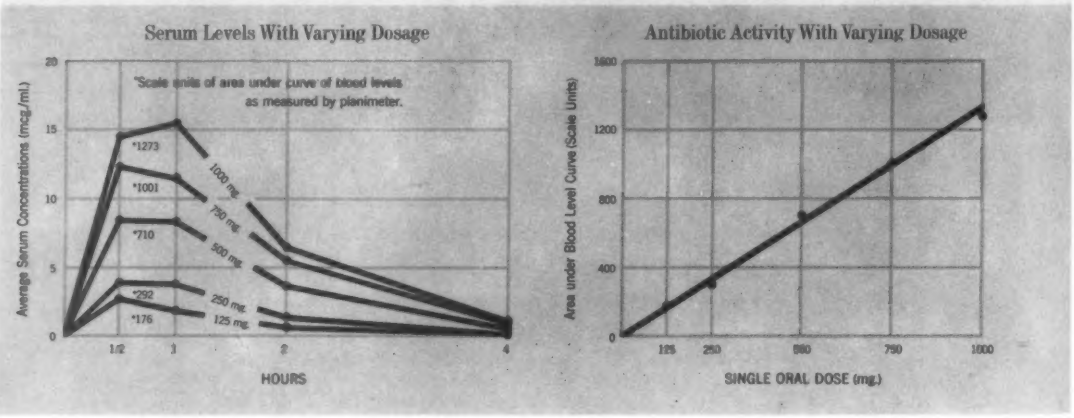
FIGURE 5—Effect of Staphylococcal Penicillinase on Different Penicillins



ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSAGE

Cronk[5] studied blood levels after administering varying amounts of SYNCILLIN. (Figure 6.) Total antibiotic activity (obtained by measuring areas under curves with a planimeter) increases rapidly as the dose is doubled. These data show that increased dosage markedly increases serum concentration and thus may enhance the drug's effectiveness.

FIGURE 6



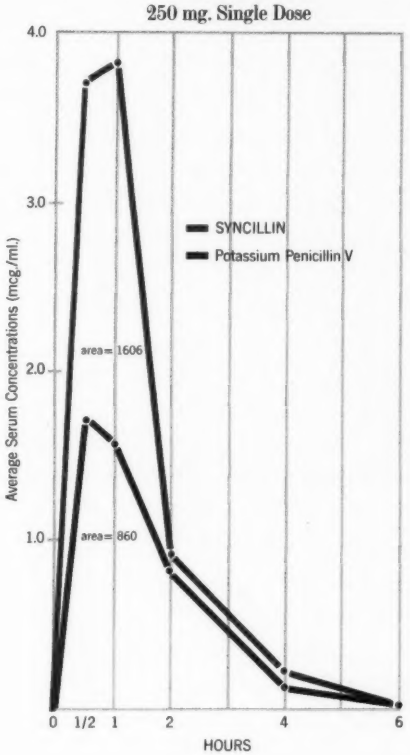
BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V AFTER ORAL ADMINISTRATION

Wright[6] performed comparative crossover blood level studies on volunteer subjects receiving equivalent amounts of potassium penicillin V and SYNCILLIN. The peak concentrations attained during the first hour after administration were twice as high with SYNCILLIN.

The total antibiotic activity as measured by the area under the curves (see Figure 7) indicates an almost 2 to 1 superiority of SYNCILLIN (1606) over potassium penicillin V (860).

The higher blood levels may be of value with organisms of only moderate penicillin-sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition these higher levels may be necessary where there is infection in areas with a poor blood supply.[7] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue.

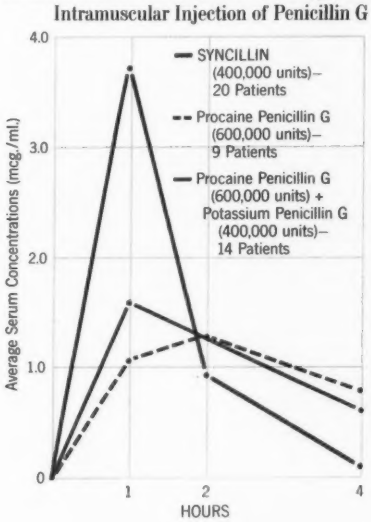
FIGURE 7
20 Subject Crossover
250 mg. Single Dose



BLOOD LEVELS MUCH HIGHER THAN WITH INTRAMUSCULAR PENICILLIN G

In addition, blood levels attained with oral SYNCILLIN[6] are much higher than those with intramuscular penicillin G.[8a, b] (See Figure 8.) Note that the level at one hour for SYNCILLIN (3.8 mcg./ml.) is more than twice as high as with procaine penicillin G, even when reinforced with potassium penicillin G (1.6 mcg./ml.). Since penicillins are *bactericidal,* these intermittent high serum levels can be clinically significant. Thus, SYNCILLIN offers the promise of superior efficacy via the safer oral route.

FIGURE 8—Serum Levels after Oral Administration of SYNCILLIN (250 mg.) and after Intramuscular Injection of Penicillin G



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

SYNCILLIN has been administered in multiple doses to 437 patients and volunteers. One patient developed itching during therapy, possibly an allergic side effect. Another had a purpuric rash, but no relationship to SYNCILLIN was established. No reactions were observed in 9 patients with a known history of sensitivity to penicillin.

While the above data suggests the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *The usual precautions for oral penicillin therapy should be observed.* Patients with histories of asthma, hay fever, urticaria, or previous penicillin-sensitivity should especially be watched carefully. Since SYNCILLIN is administered orally, it may be expected to be safer than parenteral penicillin.

As Flippin[9] recently stated, "... it is well established that serious allergy to the drug [penicillin] is most likely to occur following parenteral administration, especially after repeated intramuscular injections; the oral route is least likely to initiate severe hypersensitivity reactions. This can be explained partly by the fact that when reactions develop following oral medication, they are usually slow enough to treat symptomatically; thus the progression of the reaction can usually be interrupted. . . . In view of the relatively high incidence of severe allergy to injectable penicillin, it would seem advisable to employ oral penicillin routinely, except in the control of infections involving the blood stream, endocardium, meninges, etc., in which cases the parenteral route remains the preferred treatment."

SYNCILLIN, like other penicillins, is essentially free of other toxicity. No hematopoietic, hepatic, or renal toxicity was observed in 210 volunteers receiving 1 gm. daily for 2 to 3 weeks.[10]

CLINICAL EFFICACY DEMONSTRATED IN PENICILLIN-SENSITIVE INFECTIONS

Clinical trials conducted by Blau and Kanof,[11] White,[12] Prigot,[13] Robinson,[14] Dube,[15] Ferguson,[16] Rutenburg,[17] Richardson,[18] Bunn,[19] Cronk,[5] Kligman,[10] and Yow [20] demonstrated the efficacy of SYNCILLIN in a variety of streptococcal, staphylococcal, pneumococcal, and gonococcal infections. Conditions treated included respiratory, skin, soft tissue, wound, and chronic urinary tract infections; acute gonorrhea; cellulitis; septicemia; otitis media; gingivitis; and Vincent's angina. In a few patients SYNCILLIN was used for rheumatic fever or gonorrheal prophylaxis.

One hundred seventy-two of one hundred ninety-six patients responded favorably to SYNCILLIN. The failures included 1 patient with pustular dermatoses, 10 elderly patients with chronic urinary tract infections, 1 patient with gonorrhea, 1 patient with a gram-negative infection, and 10 patients with staphylococcal infections. Lack of response of staphylococcal infections was attributed to the presence of resistant organisms or local suppurative foci requiring drainage.

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Relatively few side effects were encountered. One patient experienced moderate itching of the skin which was controlled by an antihistamine. Another reported pruritus ani which did not interfere with therapy. Diarrhea occurred in 4 instances. There was one purpuric rash, but no relationship to SYNCILLIN could be established.

Clinical response usually begins within 24 hours in infections susceptible to SYNCILLIN. Recovery occurs in 4 to 7 days depending upon the severity of the infection. Gonorrheal infections respond very promptly to SYNCILLIN; 500 mg. b.i.d. for two days usually produce bacteriologic cures.

IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

SYNCILLIN is a mixture of isomers. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. Furthermore, the D- and L-isomers have other distinguishing chemical, pharmacological, and microbiological properties. Their *in vivo* and *in vitro* activities differ for many important pathogens. *Against many of the organisms tested, the combination of isomers* (SYNCILLIN) *is much more active than the stronger isomer alone.* This phenomenon of isomeric complementarity is not always demonstrable, for in a few instances SYNCILLIN is slightly less active.

Isomeric complementarity has previously been demonstrated *in vitro* (Figure 4) and *in vivo* (Figure 1). Figure 9 reveals a third form of superiority related to isomeric complementarity. Equal concentrations of SYNCILLIN and penicillin V were required to inhibit this growth of staphylococci *in vitro.* But, *in vivo,* a much smaller amount of SYNCILLIN *(one-third that of penicillin V)* was effective in an experimental infection with the same strain. These observations on complementary action indicated the advantage of producing the mixture of isomers as the medication to be made available for clinical therapy.

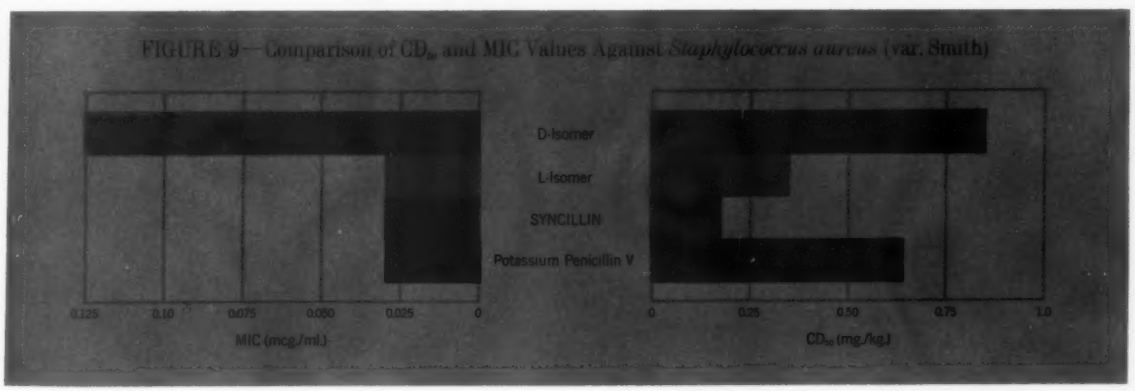


FIGURE 9—Comparison of CD_{50} and MIC Values Against *Staphylococcus aureus* (var. Smith)

Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figures 1 and 9)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

— *staphylococcal penicillinase antibiotic inactivation (Figure 5)*

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Indications:

SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins.

SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage:

125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals.

Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

Precautions:

While present data suggest the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *Therefore the usual precautions with oral penicillin therapy must be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, the interval between dosages should be lengthened.

If superinfection occurs during therapy, appropriate measures should be taken.

Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply:

125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

References: 1. Lein, J.: Microbiology report to Bristol Laboratories Inc. 2. Wright, W. W.: Microbiology report to Bristol Laboratories Inc. 3. White, A. C.: Microbiology report to Bristol Laboratories Inc. 4. Dubos, R. J.: Bacterial and Mycotic Infections of Man, 3rd edition, Philadelphia, J. B. Lippincott Co., p. 690. 5. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 6. Wright, W. W.: Clinical report to Bristol Laboratories Inc. 7. Kass, E. H.: Am. J. Med. *18*:764 (May) 1955. 8a. White, A. C.; Couch, R. A.; Foster, F.; Calloway, J.; Hunter, W., and Knight, V.: in Welch, H. and Marti-Ibañez, F.: Antibiotics Annual — 1955-1956, Medical Encyclopedia, Inc., New York, 1956, p. 490. b. Data on file — at Bristol Laboratories. 9. Flippin, H. F.: Pennsylvania M. J. *62*:864 (June) 1959. 10. Kligman, A.: Clinical report to Bristol Laboratories Inc. 11. Blau, S., and Kanof, N.: Clinical report to Bristol Laboratories Inc. 12. White, A. C.: Clinical report to Bristol Laboratories Inc. 13. Prigot, A.: Clinical report to Bristol Laboratories Inc. 14. Robinson, C.: Clinical report to Bristol Laboratories Inc. 15. Dube, A. H.: Clinical report to Bristol Laboratories Inc. 16. Ferguson, B.: Clinical report to Bristol Laboratories Inc. 17. Rutenburg, A. M.: Clinical report to Bristol Laboratories Inc. 18. Richardson, J. H.: Clinical report to Bristol Laboratories Inc. 19. Bunn, P. A.: Clinical report to Bristol Laboratories Inc. 20. Yow, E. M.: Clinical report to Bristol Laboratories Inc.

BRISTOL

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SYNCILLIN

WHITE'S VITAMIN A & D OINTMENT

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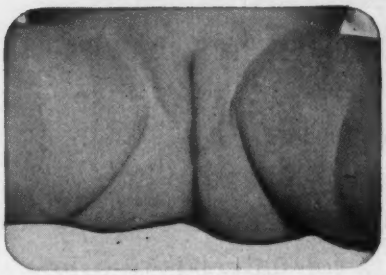
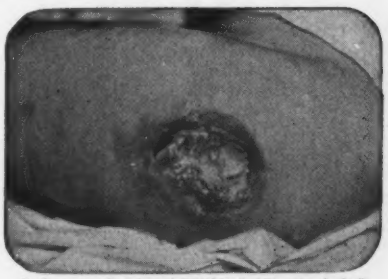
Before application of White's Vitamin A & D Ointment—Typical diaper rash with excoriation of skin.



After application of White's Vitamin A & D Ointment at every diaper change—Diaper rash has completely disappeared within one week.

Before application of White's Vitamin A & D Ointment—Treatment-resistant varicose ulcer in elderly obese patient.

After daily treatment with White's Vitamin A & D Ointment—Completely healed ulcer photographed five weeks after the start of treatment with White's Vitamin A & D Ointment.



Before applications of White's Vitamin A & D Ointment—Severe pressure sore in area over greater tuberosity of femur.

After daily treatment with White's Vitamin A & D Ointment—The sore is now filled with granulation tissue and shows signs of re-epithelization at margins.

Supplied in 1½ and 4 oz. tubes; 1 lb. jars and 5 lb. containers.

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

When you want equanimity, don't settle for somnolence

Somnolence is no longer inseparable from equanimity. Levanil has relegated it, in this connection, to the status it has always deserved: that of a side effect.

Levanil is not a hypnotic, a muscle relaxant, or a hypotensive agent. It does not isolate or insulate the patient.

Its sole effect is to promote equanimity: a state of mind in which the patient is emotionally equal to the task of recognizing and accepting reality with intelligence and good grace.

Try it in those cases where your clinical objective is equanimity, but not somnolence.

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The Upjohn Company
Kalamazoo, Michigan

Levanil*

Available:
300 mg. tablets in bottles of 50.

Dosage:
Adults, ½ to 1 tablet 3 or 4 times a day.
Children, ½ tablet 3 or 4 times a day.

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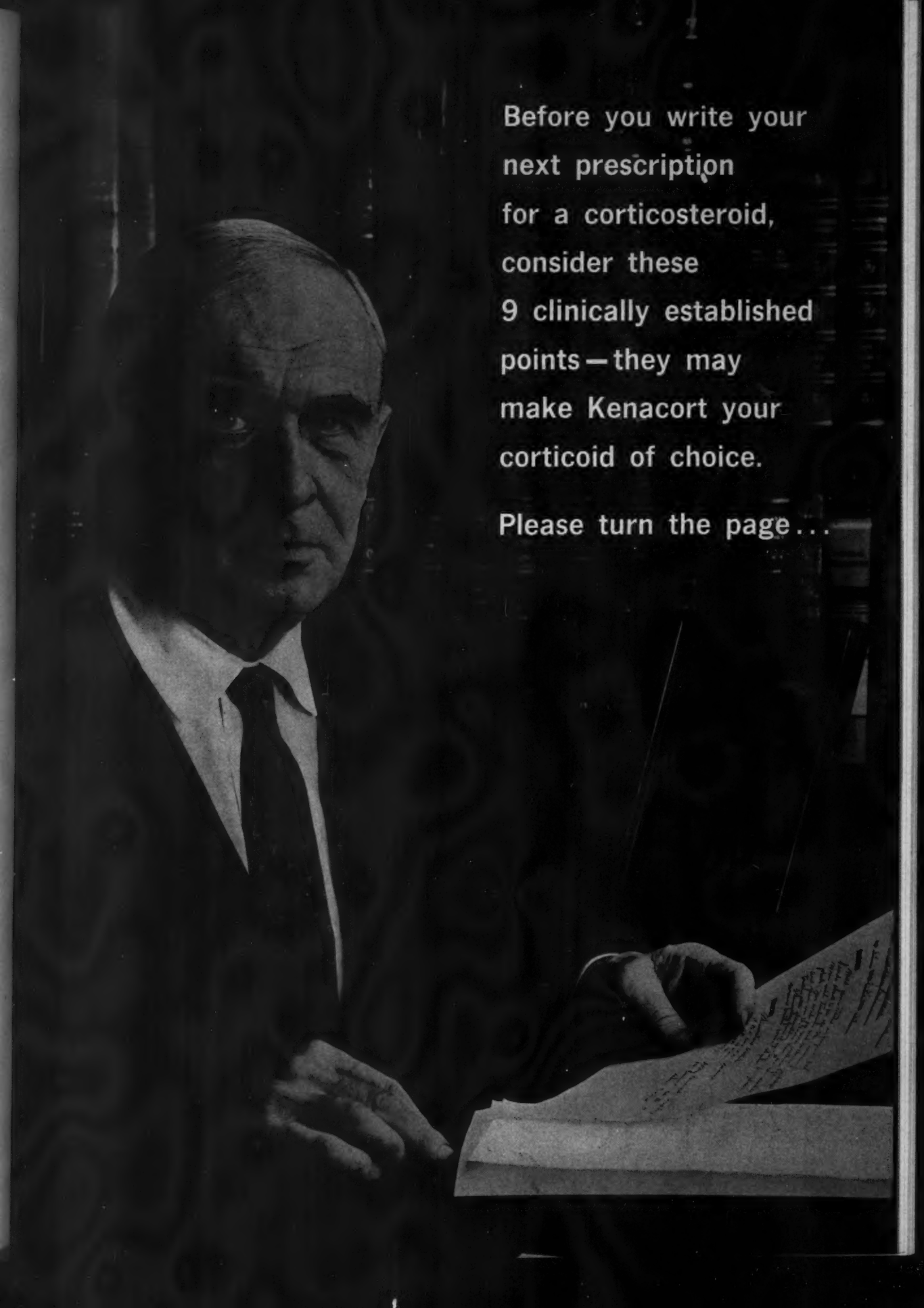

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Allison, J. R., Sr., and Allison, J. R., Jr.: Monographs on Therapy 3:99 (Oct.) 1958.

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Feinberg, S. M.; Feinberg, A. R., and Fisherman, E. W.: J. A. M. A. 167:58 (May 3) 1958.

pre-prescription point number **3**

no sodium or water retention—low salt diet not necessary

Hartung, E. F.: J. A. M. A. 167:973 (June 21) 1958.

pre-prescription point number **4**

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Council on Drugs: J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **5**

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Bongiovanni, A. M.; Heilman, W. J., and Eberlein, W. R.: J. Pediat. 53:3 (July) 1958.

pre-prescription point number **6**

no secondary hypertension—no significant change in pulse, respiration, or blood pressure

Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J. A. M. A. 167:959 (June 21) 1958.

Bernsten, C. A., Jr., and others: New York Rheumatism Association, Annual Meeting, New York, April 9, 1959.

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Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:
J. A. M. A. 167:959 (June 21) 1958.
Council on Drugs:
J. A. M. A. 169:257 (Jan. 17) 1959.

pre-prescription point number **9**

gastrointestinal complaints infrequent

Hartung, E. F.:
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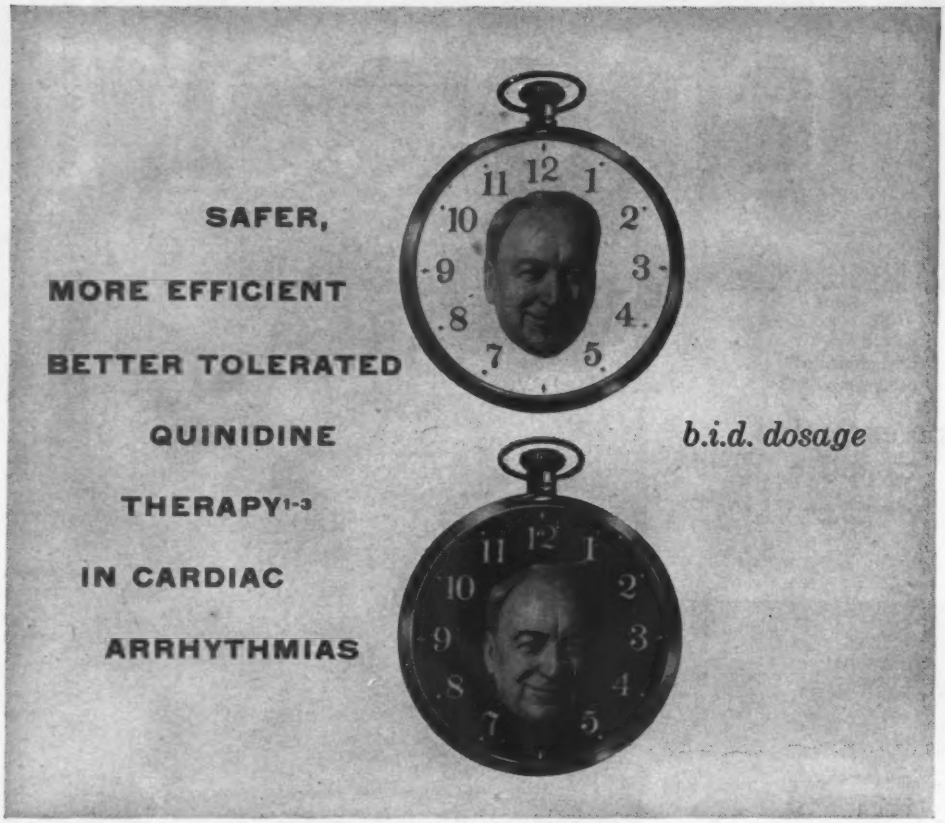

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1. Bellet, S.: Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1214, 1958.

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IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY–Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females[1]—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

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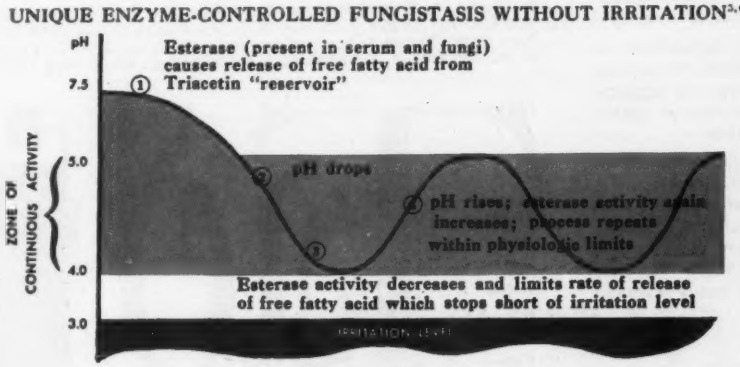
UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION[5,6]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Esterase (present in serum and fungi) causes release of free fatty acid from Triacetin "reservoir"
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References: 1. Idson, B.: Drug & Cosmetic Industry *84*:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. *28*:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy *7*:172 (Apr.) 1957.

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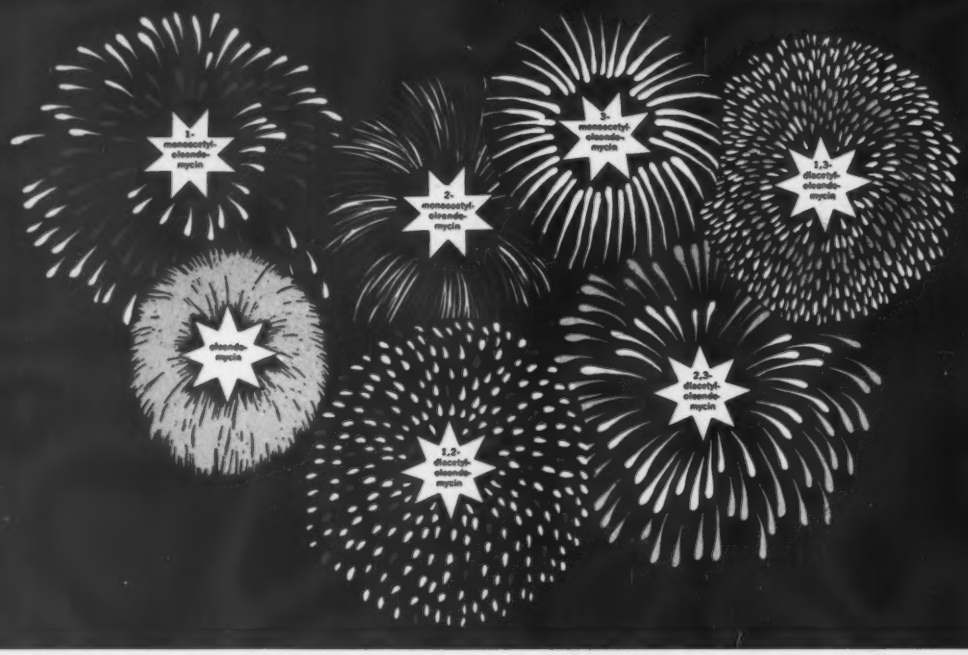

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Supplied: TAO Capsules—250 mg., and 125 mg., bottles of 60. **TAO for Oral Suspension**—125 mg. per tsp. (5 cc.) when reconstituted; unusually palatable cherry flavor; 60 cc. bottle. Prescription only.

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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

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reduces postnasal drainage — lessens pharyngeal irritation
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pheniramine maleate	6.25 mg.
pyrilamine maleate	6.25 mg.)
Dormethan (brand of dextromethorphan HBr)	15 mg.
Ammonium chloride	90 mg.

Dosage (to be administered every 3 or 4 hours): *Adults*—2 tsp.; *Children 6 to 12*—1 tsp.; *1 to 6*—½ tsp.; *under 1*—¼ tsp. One dose at bedtime is usually sufficient to control the cough cycle initiated by postural drainage of paranasal sinuses.

References: 1. Bickerman, H. A.: in Drugs of Choice, Mosby, St. Louis, 1958, p. 557. 2. Lhotka, F. M.: Illinois M. J. *112*:259 (Dec.) 1957. 3. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958. 4. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958.

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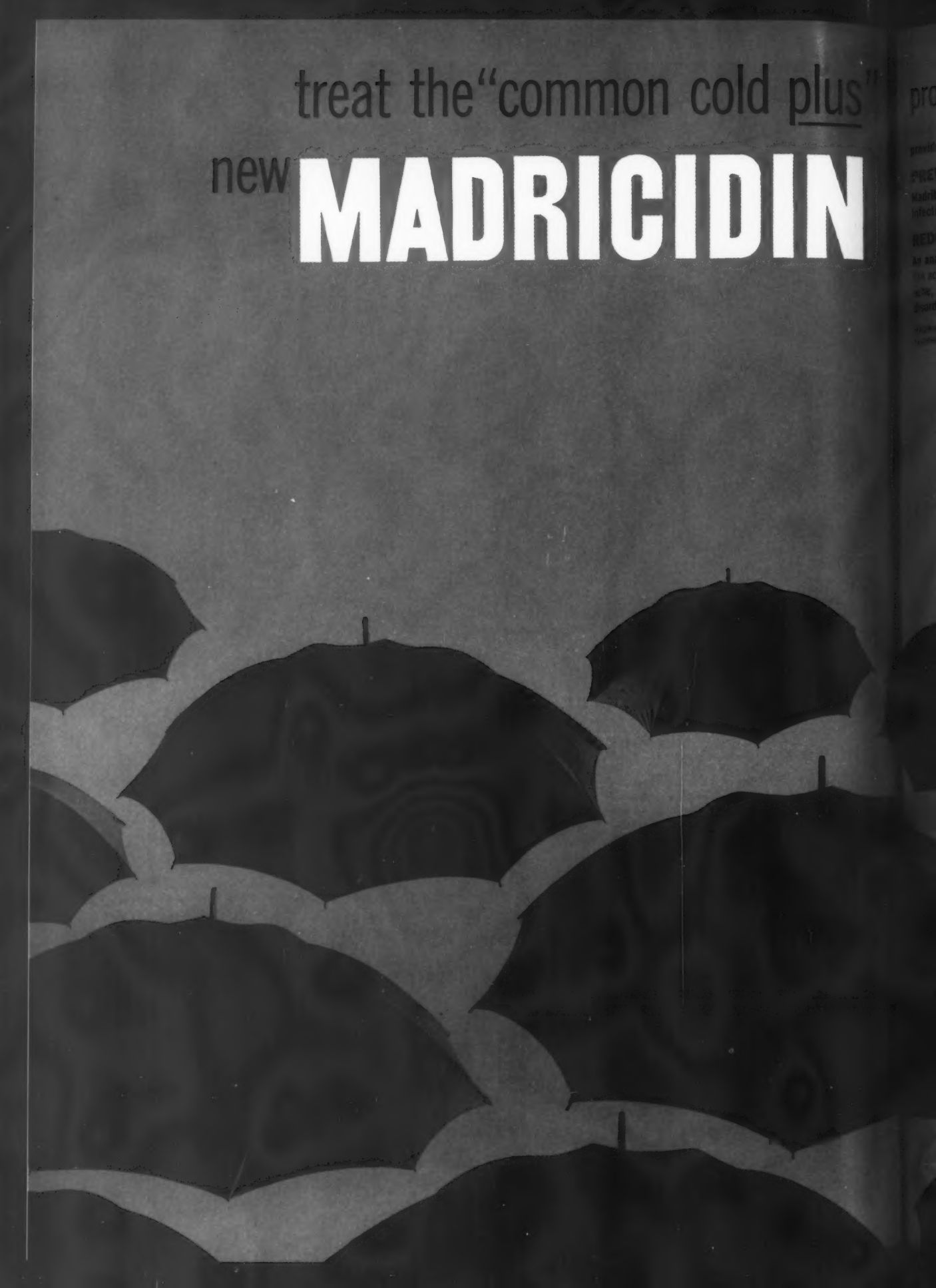

prompt symptomatic relief plus defense against secondary invaders

provides these therapeutic actions:

PREVENTS SECONDARY BACTERIAL INFECTIONS

Madribon (125 mg per capsule), the low dosage sulfonamide, avoids infections which may complicate the common cold

REDUCES FEVER AND RELIEVES HEADACHE

An analgesic-antipyretic, N-acetyl-p-aminophenol (120 mg)...considered the active metabolite of acetophenetidin...reduces fever, relieves headache, myalgia, and other discomforts associated with acute respiratory disorders

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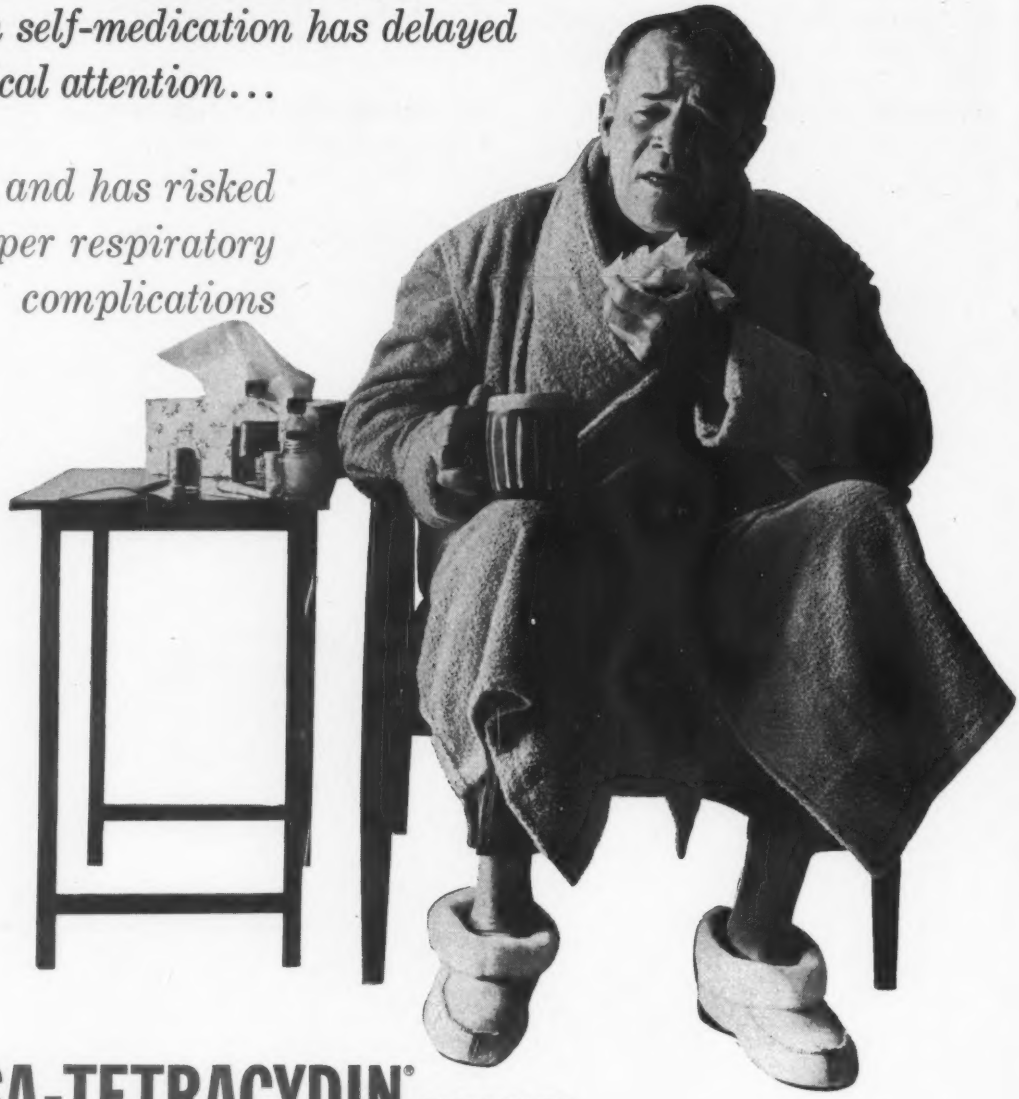
when self-medication has delayed medical attention...

...and has risked upper respiratory complications



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Cosa-Tetracyn® – analgesic – antihistamine compound

act quickly to

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each capsule contains:

Cosa-Tetracyn	125 mg.
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caffeine	30 mg.
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QUESTION:

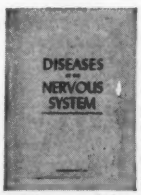
What have authorities reported as to the efficacy of Fiorinal in tension headache?

ANSWERS:

From the published reports of leading clinicians.

"The most effective symptomatic medication in the treatment of tension headache have been several analgesic and sedative combinations. One of the most effective is Fiorinal, which yielded relief in two out of three patients." *(Friedman, A. P., von Storch, T. J. C. and Merritt, H. H.: Neurology 4:773, Oct. 1954.)*

"In the treatment of tension headaches... [Fiorinal's non-narcotic action] offers a better opportunity for relief than some usually prescribed non-narcotic analgesics." *(Weisman, S. J.: Am. Pract. & Digest. Treat. 6:1019, July 1955.)*



"Fiorinal appears to be one of the most useful preparations to date for the relief of tension headaches. Easing of the head discomfort was accomplished by one or two tablets without any unpleasant side effects such as drowsiness or gastric upsets. In many cases Fiorinal appeared to temporarily relieve the discomfort from sinus trouble or acute respiratory infections." *(Kibbe, M. H.: Dis. Nerv. System 16:77, March 1955.)*

specific therapy for tension headache

Fiorinal®

relieves pain, muscle spasm, nervous tension

rapid action • non-narcotic • economical

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Each tablet contains:
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Dosage: **1 or 2 tablets every 4 hours, according to need, up to 6 per day.**

SANDOZ

mental and emotional stress

surgery

pain of cancer

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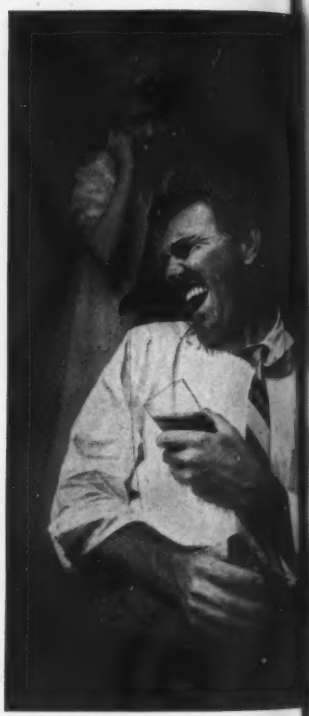

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Thorazine®... one of the fundamental drugs in medicine

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can control the agitated, hostile senile and help her live a composed and useful life.

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Polio IMMUNE GLOBULIN

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MODIFIES—permits a mild attack followed by natural immunity

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CONCENTRATED—2 cc. is equivalent to 40 cc. normal immune serum derived from adult venous blood

Also recommended for prevention of infectious hepatitis, passive immunity against paralytic poliomyelitis, may be useful for passive immunity against maternal rubella, and as an adjunct to antibiotic therapy. May be beneficial for oral herpetiform lesions.*

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*Council on Drugs: J.A.M.A. *168*:183 (Sept. 13) 1958.

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Metabolic acidosis
Laboratory evaluation and calculation of alkali deficits*

RONALD L. SEARCY, Ph.D.,† and *LOIS M. BERGQUIST, M.S.*,‡ *Departments of Pathology, Los Angeles County Osteopathic Hospital, and College of Osteopathic Physicians and Surgeons, Los Angeles, California*

No single laboratory test has yet been devised which can accurately establish the presence of metabolic acidosis. Attempts are often made to use a carbon dioxide (CO_2) determination for this purpose. This term is extremely ambiguous since it may refer to a measurement of the total CO_2 content,[1] the CO_2 capacity,[2] the CO_2 combining power,[3] the CO_2 combining capacity, or the serum bicarbonate (HCO_3).[4] The total CO_2 content or capacity measures the HCO_3, CO_2, and carbonic acid (H_2CO_3) in serum. However, the CO_2 combining power and the serum HCO_3 titrations assess only HCO_3 ion concentrations. The use of the term "CO_2 combining capacity" leads to even greater confusion since it can denote either a CO_2 capacity or combining power. Therefore, not only is the term "CO_2 determination" meaningless, but it cannot be used to evaluate accurately states of acidosis or alkalosis. Systemic acid-base balance has best been defined by Henderson[5] and Hasselbalch in terms of blood pH, serum HCO_3, and dissolved CO_2 concentrations. The relationships between these three variables have been expressed as follows:

$$\text{pH} = \text{p}k' + \log \frac{\text{serum HCO}_3}{\text{dissolved CO}_2}$$

*This work has been supported in part by a research grant from the United States Public Health Service, Project A-3213, and the Attending Staff Association of the Los Angeles County Osteopathic Hospital.
†Clinical Biochemist, Los Angeles County Osteopathic Hospital, and Associate Professor of Pathology, College of Osteopathic Physicians and Surgeons, Los Angeles.
‡Bacteriologist, Los Angeles County Osteopathic Hospital, and Visiting Assistant Professor, Department of Pathology, College of Osteopathic Physicians and Surgeons, Los Angeles.

Since the pk' is a constant (6.1), two of the three remaining factors must be known before the equation can be solved. As yet, it is not practical to estimate the amounts of dissolved CO_2 in the blood. Blood pH and serum HCO_3 determinations must be carried out in order to arrive at a value for this form of CO_2.

This report describes simple and accurate methods for the measurement of serum HCO_3 and blood pH which then makes possible the calculation of the dissolved CO_2. However, the necessity for computing dissolved CO_2 values at particular pH and HCO_3 levels has been eliminated. This has been accomplished through formulation of a table which defines all states of acid-base equilibrium in terms of the Henderson-Hasselbalch relationships.

Severe and often unrecognized metabolic acidosis is shown in this report to be associated with various clinical conditions. In these instances, the Henderson-Hasselbalch equation has been demonstrated to be the only sound basis for adequate repair therapy. A simple method for calculation of the alkali deficit has been devised which provides for the therapeutic use of sodium bicarbonate ($NaHCO_3$) or lactate.

Materials and methods

Determination of serum bicarbonate • Reagents used are as follows:

Hydrochloric acid. A 0.02N solution is prepared by diluting 5.0 ml. of stock 1N hydrochloric acid to 250 ml. with distilled water. The exact normality of the dilute acid is determined by a titration with standardized alkali.

Sodium hydroxide. A 0.02N solution is prepared by diluting 5.0 ml. of stock 1N sodium hydroxide to 250 ml. with distilled water. The dilute alkaline solution is standardized with the 0.02N hydrochloric acid. This preparation is kept tightly stoppered and is renewed frequently.

Caprylic alcohol. An analytical reagent grade is used.

Neutral red indicator. An 0.065 percent solution is prepared by dissolving 65 mg. of the dye in 100 ml. of 50 percent ethyl alcohol.

The procedure used is as follows: A 2.0 ml. aliquot of serum is placed in a 125 ml. Erlenmeyer flask and diluted with exactly 5.0 ml. of 0.02N hydrochloric acid. A drop of caprylic alcohol is added and the serum-acid mixture is swirled for several seconds to remove the generated CO_2. The mixture is diluted with approximately 20 ml. of distilled water, and 0.3 ml. of neutral red indicator is added. The amount of 0.02N hydrochloric acid not utilized in the reaction with serum HCO_3 is determined by a titration with 0.02N sodium hydroxide to a salmon-pink end-point. The number of milliliters of base utilized, subtracted from the amount of acid added, times 10, is equivalent to the serum HCO_3 expressed in milliequivalents per liter. Using this technic normal values range from 24 to 32 mEq./L. for adults and from 18 to 24 mEq./L. for children.

Determination of blood pH • Collection of blood specimen is done according to a standardized procedure. Many workers[6,7] recommend that blood be drawn and kept under paraffin oil to prevent the loss of CO_2. However, recent studies strongly suggest that this technic is subject to significant error.[8-10] Therefore, the drawing of blood in a heparinized syringe without oil is the technic of choice. Blood collected in this manner can be stored at room temperature for as long as 30 minutes without significantly altering the pH.[11] In an ice bath these specimens are stable for more than 4 hours.[12]

Measurement of the hydrogen (H) ion concentration is performed as follows: A Beckman pH meter (model G) is standardized with buffer solutions having a known pH of 7.00, 7.40, and 7.80.[13] Several milliliters of a blood specimen are transferred from the syringe to a 5.0 ml. beaker and placed in contact with the electrodes. This brief exposure to air does not significantly alter the pH. Meter readings are interpolated to the nearest 0.01 of a pH unit. At this time the temperature of the blood is also taken and recorded. The observed pH of the blood must be corrected to 38 C. or to the temperature of the patient by use of the following equation:

$$pH_c = pH_o - [0.0147\ (38\ C. - T)]$$

T = Temperature of the blood at the time of the pH measurement

pH_o = The pH observed on the meter

pH_c = The pH corrected to 38 C.

The pH_c varies normally from 7.35 to 7.45.

Results and discussion

Limitations of HCO_3 and pH tests • Although it is widely used, the serum HCO_3 determination in itself has limited value in defining acidotic or alkalotic states. Figure 1 demonstrates that in various acid-base imbalances the circulating HCO_3 levels are independent of the blood H ion concentrations. In either acidosis or alkalosis the serum HCO_3 values may be high or low depending upon whether or not the imbalance is metabolic or respiratory. In respiratory acidosis and metabolic alkalosis, for example, serum HCO_3 levels are usually elevated. On the other hand, reductions of this alkali fraction are associated with respiratory alkalosis or metabolic acidosis.

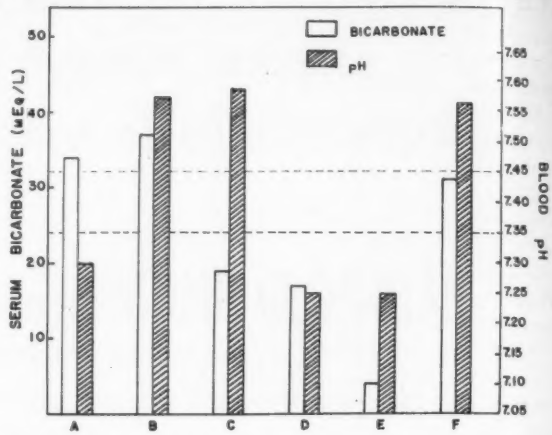

FIG. 1: Relationships of serum HCO_3 to blood pH in acid-base imbalances: **A**, respiratory acidosis; **B**, metabolic alkalosis; **C**, respiratory alkalosis; **D**, metabolic acidosis; **E**, respiratory acidosis and metabolic acidosis; and **F**, respiratory alkalosis and metabolic alkalosis.

It is therefore impossible to predict the pH of the blood solely on the basis of the serum HCO_3 concentration.

The blood pH measurement is the only single laboratory test diagnostic for acidosis or alkalosis. However, it provides no information concerning the respiratory or metabolic nature of the imbalance. The H ion concentration reveals only the degree of acidosis or alkalosis.

The unreliability of serum HCO_3 determinations as an indicator of acid-base equilibrium was demonstrated in 16 hospital patients (Table I). The first 8 patients exhibited serum HCO_3 values within the normal range of 24 to 32 mEq./L. However, the pH of blood in this group of patients varied from 7.21 to 7.78. These data indicate clearly that a profound acidosis or alkalosis may be present despite the fact that serum HCO_3 concentrations are normal. Patients 5 and 7 demonstrate strikingly the lack of correlation between the serum HCO_3 level and the blood pH. Although these two individuals had the same serum HCO_3 concentration, patient 5 was in a state of

TABLE I—SERUM HCO_3 AND BLOOD pH VALUES OBSERVED IN HOSPITAL PATIENTS

Case number	Serum HCO_3 (mEq./L.)	Blood pH	Case number	Serum HCO_3 (mEq./L.)	Blood pH
1	30	7.25	9	45	7.40
2	26	7.78	10	40	7.36
3	26	7.55	11	43	7.35
4	32	7.61	12	21	7.40
5	31	7.21	13	19	7.35
6	24	7.51	14	18	7.35
7	31	7.59	15	20	7.44
8	27	7.51	16	15	7.40

frank acidosis while patient 7 had marked alkalosis. Patients 9 through 16 had either abnormally high or low amounts of serum HCO_3. However, the pH in each case was within the normal limits of 7.35 to 7.45. Although patients 9 and 12 had the same H ion concentration, the serum HCO_3 values were 45 and 21 mEq./L., respectively.

These findings serve to substantiate the fact that acid-base status cannot be evaluated solely on the basis of circulating HCO_3, but is dependent on the HCO_3/CO_2 ratio. Therefore, a third variable, the dissolved CO_2 concentration, must be known for a complete acid-base assessment in terms of the Henderson-Hasselbalch equation.

Computation of dissolved CO_2 • For example, it a patient has a pH of 7.10 and a serum HCO_3 of 15 mEq./L., the dissolved CO_2 can be computed as follows:

$$pH = pk' + \log \frac{\text{serum } HCO_3}{\text{dissolved } CO_2}$$

$$7.1 = 6.1 + \log \frac{15}{CO_2}$$

$$7.1 = 6.1 + \log 15 - \log CO_2$$

$$\log CO_2 = 6.1 + 1.8 - 7.1$$

$$\log CO_2 = 0.8$$

$$\text{dissolved } CO_2 = 1.5 \text{ mEq./L.}$$

The solution of this equation requires one logaritnmic and one antilogarithmic function. The mathematics involved are time-consuming, and log tables are not always available. Therefore, the Henderson-Hasselbalch equation has been solved using a serum HCO_3 range of 5 to 50 mEq./L at pH intervals from 6.8 to 7.8 (Table II, see pp. 340, 341). The amount of dissolved CO_2 can be quickly ascertained by following appropriate pH and serum HCO_3 columns. All clinical situations of acid-base equilibrium are thus defined in terms of the Henderson-Hasselbalch formula. The dissolved CO_2 values that are associated with the normal pH and HCO_3 levels are contained within the solid lines on the table. In this area the dissolved CO_2 can vary normally from 1.1 to 1.8 mEq./L. In the adjacent areas within the broken lines the dissolved CO_2 values accompany increases or decreases in serum HCO_3 concentrations. However, since the pH remains normal these points represent states of complete compensation.

This table may also be used to describe all uncompensated alkalotic and acidotic conditions in terms of HCO_3, dissolved CO_2, and pH. Table III demonstrates that certain mixed acid-base states can be diagnosed only when the amounts of circulating dissolved CO_2 are established. Pure metabolic acidosis and that associated with respiratory acidosis may have serum HCO_3 and pH ranges which overlap. However, much higher dissolved CO_2 values are found when respiratory acidosis is superimposed upon metabolic acidosis. Again the dissolved CO_2 levels may be the most useful criteria for distinguishing a pure metabolic alkalosis from that found with respiratory alkalosis.

TABLE III—DEFINITION OF ACID-BASE IMBALANCES IN TERMS OF SERUM HCO_3, DISSOLVED CO_2, AND BLOOD pH

Clinical condition	pH	Serum HCO_3 (mEq./L.)	Dissolved (CO_2) (mEq./L.)
Metabolic acidosis	6.80-7.34	5-24	0.3- 1.8
Metabolic acidosis and respiratory acidosis	6.80-7.16	10-24	1.9- 4.6
Respiratory acidosis	6.80-7.34	24-32	1.4- 6.5
Respiratory acidosis and metabolic alkalosis	6.80-7.34	32-50	1.9-10.0
Metabolic alkalosis	7.48-7.80	32-50	1.0- 1.4
Metabolic alkalosis and respiratory alkalosis	7.48-7.80	32-46	0.6- 0.9
Respiratory alkalosis	7.48-7.80	24-32	0.4- 1.4
Respiratory alkalosis and metabolic acidosis	7.48-7.80	5-24	0.1- 1.0

Clinical applications

A fundamental metabolic acidosis is common to a variety of clinical conditions. Such an imbalance may be therapeutically induced, a toxicologic response, or related to a systemic disorder.

Salicylate intoxication • Hyperventilation may either contribute to respiratory alkalosis or result from metabolic acidosis. Therefore, some confusion has existed concerning interpretation of the marked hyperpnea generally observed in salicylism. To elucidate the respiratory mechanism, Singer[14] has examined changes in blood pH and serum HCO_3 levels subsequent to salicylate ingestion. He concludes that initially the hyperpnea causes a loss of dissolved CO_2 with a resultant respiratory alkalosis. Hyperpnea has been demonstrated by others[15,16] to be a direct effect of this analgesic upon respiration centers.

During the phase of respiratory alkalosis both the dissolved CO_2 and HCO_3 concentrations are greatly reduced. This in turn lowers the total circulating buffer capacity which makes the blood extremely vulnerable to any H ion donor such as salicylate. Ketonemia results since this drug impairs the metabolism of carbohydrate and promotes the oxidation of fat. The accumulation of ketone bodies further reduces serum HCO_3 levels. With the reduction in HCO_3, the HCO_3/CO_2 ratio is decreased and acidemia ensues. It is this metabolic acidosis quickly following the respiratory alkalosis which is usually the lethal complication associated with salicylism. Therefore, to establish the magnitude of the acidotic state, Segar and Holliday[17] in a recent article stress the importance of obtaining serial blood pH and serum HCO_3 determinations.

It has been recognized for some time that salicylate intoxication and diabetic acidosis frequently present a similar clinical picture.[18,19] An early differential diagnosis may be hampered since patients suffering from either condition exhibit hyperventilation, dehydration, ketosis, polydypsia, and apparent hyperglycemia and glycosuria. However, the observance of an elevated blood pH in the early phases of salicylism may eliminate hypoinsulinism as a causal factor. Without resorting to toxicologic technics it may

TABLE II—RELATIONSHIP OF BLOOD pH AND SERUM BICARBONATE TO DISSOLVED

	5	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
6.80	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0	4.2	4.4	4.6	4.8	5.0	5.1	5.4
.82	1.0	1.1	1.4	1.5	1.7	1.9	2.1	2.3	2.5	2.7	2.9	3.0	3.2	3.5	3.6	3.8	4.0	4.2	4.4	4.6	4.8	4.9	5.1
.84	0.9	1.1	1.3	1.5	1.6	1.8	2.0	2.2	2.4	2.6	2.8	2.9	3.1	3.3	3.5	3.6	3.8	4.0	4.2	4.4	4.6	4.7	4.9
.86	0.9	1.0	1.2	1.4	1.6	1.7	1.9	2.1	2.2	2.5	2.6	2.7	3.0	3.2	3.3	3.5	3.6	3.8	4.0	4.2	4.4	4.5	4.7
.88	0.8	1.0	1.2	1.3	1.5	1.7	1.8	2.0	2.1	2.4	2.5	2.6	2.8	3.0	3.2	3.3	3.5	3.6	3.8	4.0	4.2	4.3	4.5
6.90	0.8	0.9	1.1	1.3	1.4	1.6	1.7	1.9	2.1	2.2	2.4	2.5	2.7	2.9	3.0	3.2	3.3	3.5	3.6	3.8	4.0	4.1	4.3
.92	0.8	0.9	1.1	1.2	1.4	1.5	1.7	1.8	2.0	2.1	2.3	2.4	2.6	2.8	2.9	3.0	3.2	3.3	3.5	3.6	3.8	3.9	4.1
.94	0.7	0.9	1.0	1.2	1.3	1.5	1.6	1.7	1.9	2.1	2.2	2.3	2.5	2.6	2.8	2.9	3.0	3.2	3.3	3.5	3.6	3.7	3.9
.96	0.7	0.8	1.0	1.1	1.2	1.4	1.5	1.7	1.8	2.0	2.1	2.2	2.4	2.5	2.6	2.8	2.9	3.0	3.2	3.3	3.5	3.6	3.7
.98	0.7	0.8	0.9	1.1	1.2	1.3	1.5	1.6	1.7	1.9	2.0	2.1	2.2	2.4	2.5	2.6	2.8	2.9	3.0	3.2	3.3	3.4	3.6
7.00	0.6	0.7	0.9	1.0	1.1	1.3	1.4	1.5	1.6	1.8	1.9	2.0	2.1	2.3	2.4	2.5	2.6	2.8	2.9	3.0	3.2	3.2	3.4
.02	0.6	0.7	0.9	1.0	1.1	1.2	1.3	1.5	1.6	1.7	1.8	1.9	2.1	2.2	2.3	2.4	2.5	2.6	2.8	2.9	3.0	3.1	3.2
.04	0.6	0.7	0.8	0.9	1.0	1.2	1.3	1.4	1.5	1.6	1.7	1.8	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.8	2.9	3.0	3.1
.06	0.6	0.6	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.6	1.7	1.7	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.8	2.8	3.0
.08	0.5	0.6	0.7	0.8	0.9	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8
7.10	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.8	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7
.12	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.2	1.4	1.5	1.5	1.6	1.7	1.8	1.8	2.0	2.1	2.2	2.3	2.4	2.5	2.6
.14	0.5	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.7	1.8	1.8	2.0	2.1	2.2	2.3	2.4	2.5
.16	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.7	1.8	1.8	2.0	2.1	2.2	2.2	2.4
.18	0.4	0.5	0.6	0.7	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.3	1.4	1.5	1.6	1.7	1.7	1.8	1.8	2.0	2.1	2.1	2.2
7.20	0.4	0.5	0.6	0.6	0.7	0.8	0.9	1.0	1.0	1.1	1.2	1.3	1.4	1.5	1.5	1.6	1.7	1.7	1.8	1.8	2.0	2.1	2.1
.22	0.4	0.4	0.5	0.6	0.7	0.7	0.8	0.9	1.0	1.1	1.2	1.2	1.3	1.4	1.5	1.5	1.6	1.7	1.7	1.8	1.8	2.0	2.1
.24	0.4	0.4	0.5	0.6	0.6	0.7	0.8	0.9	0.9	1.0	1.1	1.2	1.2	1.3	1.4	1.5	1.5	1.6	1.7	1.7	1.8	1.9	2.0
.26	0.4	0.4	0.5	0.6	0.6	0.7	0.7	0.8	0.9	1.0	1.1	1.1	1.2	1.3	1.3	1.4	1.5	1.5	1.6	1.7	1.7	1.8	1.9
.28	0.3	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.9	0.9	1.0	1.1	1.1	1.2	1.3	1.3	1.4	1.5	1.5	1.6	1.7	1.7	1.8
7.30	0.3	0.4	0.4	0.5	0.6	0.6	0.7	0.7	0.8	0.9	1.0	1.0	1.1	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.6	1.6	1.7
.32	0.3	0.4	0.4	0.5	0.6	0.6	0.6	0.6	0.8	0.9	0.9	1.0	1.0	1.1	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.6	1.6
.34	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.6
.36	0.3	0.3	0.4	0.5	0.5	0.5	0.6	0.6	0.7	0.8	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.2	1.3	1.3	1.4	1.4	1.5
.38	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8	0.9	1.0	1.0	1.1	1.1	1.2	1.2	1.3	1.3	1.4	1.4
7.40	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.7	0.7	0.7	0.9	0.9	1.0	1.0	1.1	1.1	1.2	1.2	1.3	1.3	1.4
.42	0.2	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.6	0.7	0.8	0.9	0.9	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.3
.44	0.2	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.6	0.8	0.8	0.9	0.9	1.0	1.0	1.1	1.1	1.1	1.2	1.2
.46	0.2	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.2
.48	0.2	0.2	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.8	0.9	0.9	1.0	1.0	1.0	1.1	1.1
7.50	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.6	0.5	0.6	0.7	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.0	1.0	1.1
.52	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.0	1.0
.54	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9	0.9	1.0
.56	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9	0.9
.58	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.4	0.5	0.6	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.8	0.9	0.9
7.60	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.8	0.9
.62	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.8	0.8
.64	0.1	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.8
.66	0.1	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.7	0.7
.68	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.7	0.7
7.70	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6	0.7
.72	0.1	0.1	0.2	0.2	0.2	0.2	0.3	0.2	0.3	0.4	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.7
.74	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6
.76	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.6
.78	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6
7.80	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.4	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5

*Serum bicarbonate (mEq./L.) is shown in boldface figures at the top of the table, pH units in italics at each end of table, and dissolved carbon dioxide (mEq./L.)

CARBON DIOXIDE, ACCORDING TO THE HENDERSON-HASSELBALCH EQUATION*

28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	
5.6	5.8	6.0	6.2	6.5	6.7	6.8	6.9	7.3	7.4	7.6	7.8	8.0	8.1	8.3	8.5	8.7	8.9	9.1	9.3	9.6	9.8	10.0	*6.80*
5.4	5.5	5.8	5.9	6.2	6.3	6.5	6.6	6.9	7.1	7.3	7.4	7.6	7.8	8.0	8.1	8.3	8.5	8.7	8.9	9.1	9.3	9.6	*.82*
5.1	5.3	5.5	5.6	5.9	6.0	6.2	6.3	6.6	6.8	6.9	7.1	7.3	7.4	7.6	7.8	8.0	8.1	8.5	8.5	8.7	8.9	9.1	*.84*
4.9	5.0	5.3	5.4	5.6	5.8	5.9	6.0	6.3	6.5	6.6	6.8	6.9	7.1	7.3	7.4	7.6	7.8	8.0	8.1	8.5	8.5	8.7	*.86*
4.7	4.8	5.0	5.1	5.4	5.5	5.6	5.8	6.0	6.2	6.3	6.5	6.6	6.8	6.9	7.1	7.3	7.4	7.6	7.8	8.0	8.1	8.5	*.88*
4.5	4.6	4.8	4.9	5.1	5.3	5.4	5.5	5.8	5.9	6.0	6.2	6.3	6.5	6.6	6.8	6.9	7.1	7.3	7.4	7.6	7.8	8.0	*6.90*
4.3	4.4	4.6	4.7	4.9	5.0	5.1	5.3	5.5	5.6	5.8	5.9	6.0	6.2	6.3	6.5	6.6	6.8	6.9	7.1	7.3	7.4	7.6	*.92*
4.1	4.2	4.4	4.5	4.7	4.8	4.9	5.0	5.3	5.4	5.5	5.6	5.8	5.9	6.0	6.2	6.3	6.5	6.6	6.8	6.9	7.1	7.3	*.94*
3.9	4.0	4.2	4.3	4.5	4.6	4.7	4.8	5.0	5.1	5.3	5.4	5.5	5.6	5.8	5.9	6.0	6.2	6.3	6.5	6.6	6.8	6.9	*.96*
3.7	3.8	4.0	4.1	4.3	4.4	4.5	4.6	4.8	4.9	5.0	5.1	5.3	5.4	5.5	5.6	5.8	5.9	6.0	6.2	6.3	6.5	6.6	*.98*
3.6	3.6	3.8	3.9	4.1	4.2	4.3	4.4	4.6	4.7	4.8	4.9	5.0	5.1	5.3	5.4	5.5	5.6	5.8	5.9	6.0	6.2	6.3	*7.00*
3.4	3.5	3.6	3.7	3.9	4.0	4.1	4.2	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.3	5.4	5.5	5.6	5.8	5.9	6.0	*.02*
3.2	3.3	3.5	3.6	3.7	3.8	3.9	4.0	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.3	5.4	5.5	5.6	5.8	*.04*
3.1	3.2	3.3	3.4	3.6	3.6	3.7	3.8	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.3	5.4	5.5	*.06*
3.0	3.0	3.2	3.2	3.4	3.5	3.6	3.6	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.3	*.08*
2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	*7.10*
2.7	2.8	2.9	3.0	3.1	3.2	3.2	3.3	3.5	3.6	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	*.12*
2.6	2.6	2.8	2.8	3.0	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	4.5	4.6	*.14*
2.5	2.5	2.6	2.7	2.8	2.9	3.0	3.0	3.2	3.2	3.3	3.4	3.5	3.6	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3	4.4	*.16*
2.4	2.4	2.5	2.6	2.7	2.8	2.8	2.9	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.6	3.6	3.7	3.8	3.9	4.0	4.1	4.2	*.18*
2.2	2.3	2.4	2.5	2.6	2.6	2.7	2.8	2.9	3.0	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.6	3.6	3.7	3.8	3.9	4.0	*7.20*
2.1	2.2	2.3	2.4	2.5	2.5	2.6	2.6	2.8	2.8	2.9	3.0	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.6	3.6	3.7	3.8	*.22*
2.1	2.1	2.2	2.2	2.4	2.4	2.5	2.5	2.6	2.7	2.8	2.8	2.9	3.0	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.6	3.6	*.24*
2.0	2.0	2.1	2.1	2.2	2.3	2.4	2.4	2.5	2.6	2.6	2.7	2.8	2.8	2.9	3.0	3.0	3.1	3.2	3.2	3.3	3.4	3.5	*.26*
1.9	1.9	2.0	2.1	2.1	2.2	2.2	2.3	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	3.0	3.0	3.1	3.2	3.2	3.3	*.28*
1.8	1.8	1.9	2.0	2.1	2.1	2.1	2.2	2.3	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	3.0	3.0	3.1	3.2	*7.30*
1.7	1.7	1.8	1.9	2.0	2.0	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	3.0	3.0	*.32*
1.6	1.7	1.7	1.8	1.9	1.9	2.0	2.0	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	*.34*
1.6	1.6	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.1	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	*.36*
1.5	1.5	1.6	1.6	1.7	1.7	1.8	1.8	1.9	2.0	2.0	2.1	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.5	2.5	2.6	2.6	*.38*
1.4	1.5	1.5	1.6	1.6	1.7	1.7	1.7	1.8	1.9	1.9	2.0	2.0	2.1	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.5	2.5	*7.40*
1.4	1.4	1.5	1.5	1.6	1.6	1.6	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.1	2.1	2.1	2.2	2.2	2.3	2.4	2.4	*.42*
1.3	1.3	1.4	1.4	1.5	1.5	1.6	1.6	1.7	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.1	2.1	2.1	2.2	2.2	2.3	*.44*
1.2	1.3	1.3	1.4	1.4	1.5	1.5	1.5	1.6	1.6	1.7	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.1	2.1	2.1	2.2	*.46*
1.2	1.2	1.3	1.3	1.4	1.4	1.4	1.5	1.5	1.6	1.6	1.6	1.7	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.0	2.1	2.1	*.48*
1.1	1.2	1.2	1.2	1.3	1.3	1.4	1.4	1.5	1.5	1.5	1.6	1.6	1.6	1.6	1.7	1.7	1.8	1.8	1.9	1.9	2.0	2.0	*7.50*
1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.3	1.4	1.4	1.5	1.5	1.5	1.6	1.6	1.6	1.6	1.7	1.7	1.8	1.8	1.9	1.9	*.52*
1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.4	1.4	1.4	1.5	1.5	1.5	1.6	1.6	1.6	1.6	1.7	1.7	1.8	1.8	*.54*
1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.6	1.6	1.6	1.6	1.7	1.7	*.56*
0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.6	1.6	1.6	1.6	*.58*
0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.3	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.6	1.6	*7.60*
0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.3	1.3	1.4	1.4	1.4	1.4	1.5	1.5	*.62*
0.8	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.3	1.3	1.3	1.3	1.4	1.4	1.4	1.4	*.64*
0.8	0.8	0.8	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.3	1.3	1.3	1.3	1.4	1.4	*.66*
0.7	0.8	0.8	0.8	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.3	1.3	1.3	1.3	*.68*
0.7	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.3	1.3	*7.70*
0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	*.72*
0.7	0.6	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.2	1.2	*.74*
0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1	*.76*
0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	0.9	0.9	0.9	1.0	1.0	1.0	1.1	1.1	*.78*
0.6	0.6	0.6	0.6	0.7	0.6	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.9	0.9	0.9	0.9	0.9	0.9	1.0	1.0	1.0	*7.80*

in lightface figures. Dissolved carbon dioxide values enclosed in box are normal; those set off by broken lines indicate states of complete compensation.

be difficult to determine the etiology of the salicylate-induced metabolic acidosis.

Renal acidosis • The metabolic acidosis accompanying kidney impairment has been arbitrarily designated to be uremic or renal tubular in origin. The decreased blood pH in uremia has been ascribed to a retention of sulfate, phosphate, and chloride ions, and to a reduction in available sodium ions. Renal tubular acidosis has been attributed to a loss of circulating HCO_3 and a failure in the tubular transfer of H ions. However, Schwartz and Relman[20] suggest that both uremia and tubular acidosis can be related to a fundamental defect in H ion excretion and HCO_3 reabsorption. Therefore, it may be possible to relate all renal acidosis to a tubular mechanism.

In renal insufficiency, the urinary losses of HCO_3 are often so severe that serum levels of this ion may be reduced as much as 50 percent of normal. One patient suffering from chronic renal disease was observed by Schwartz and his associates[21] to excrete 260 mEq. of alkali during one week. These workers found it necessary to continually administer $NaHCO_3$ in order to maintain the blood pH within normal limits. Using an infusion of 7 percent $NaHCO_3$, Reynolds and Martin[22] were able to raise serum levels of this alkali fraction from a mean of 17.5 mEq./L. to 28.3 mEq./L. Therapeutic success has been achieved by Elkinton, Squires, and Singer[23] and others[24] with sodium lactate as well as $NaHCO_3$ for correction of renal acidosis.

Diabetic coma • Ketosis regardless of etiology arises from an impairment in carbohydrate metabolism accompanied by increased fatty acid oxidation.[25] In diabetes-induced ketonemia an attempt is made by the body to utilize these acids at the expense of serum HCO_3. As this alkali fraction disappears the value of the HCO_3/CO_2 ratio is lowered and the H ion concentration of the blood is increased. Martin, Smith, and Wilson[26] point out that prolonged acidosis in the diabetic is extremely detrimental because of cellular losses of electrolytes. Enzymatic reactions are also altered when the pH is allowed to remain below normal for even short periods.[27] Therefore, any delay in treatment of acidosis may result in irreparable damage. This is supported by Danowski and coworkers,[28] who found that diabetic acidosis in children is responsible for a large percentage of preventable deaths in this age group.

Since both Na and Cl ions are lacking in diabetic coma, isotonic solutions of sodium chloride (NaCl) are frequently used during initial phases of therapy. However, Danowski[29] points out that a 1:1 ratio of Na and Cl is not physiologic. In the body these two ions are actually present in a 3:2 ratio. Therefore, a 0.9 percent saline solution may present an additional load of chloride for urinary excretion. The chloride excretory capacity may prove inadequate when a marked ketosis is associated with diabetes. Taylor[30] has found that the administration of NaCl as a repair solution may lead to a hyperchloremic acidosis superimposed upon a pre-existing metabolic acidosis. Correction of the acidosis can be more efficiently accomplished by the use of $NaHCO_3$ or sodium lactate.[31-37] These repair solutions not only promptly restore acid-base equilibrium but markedly enhance the action of insulin. Martin, Smith, and Wilson[26] have found that respiratory alkalosis is rarely a problem when these repair solutions are given to patients with marked hyperpnea. In most diabetics breathing returns to normal within a few hours after the initiation of insulin, fluid, and electrolyte therapy.

Induced diuresis • There is a growing awareness that the indiscriminate use of diuretics may be an important factor in the production of metabolic acidosis. The administration of a sulfonamide such as Diamox can cause an increased urinary excretion of HCO_3 as well as a decreased tubular reabsorption of this ion. When normal individuals received therapeutic dosages of Diamox, Hanley and Platts[38] found that urinary HCO_3 excretion was markedly increased. The serum levels of this ion fell from 25 to 19 mEq./L. during diuresis. Likewise, ammonium chloride (NH_4Cl) therapy may lead to a reduction in serum HCO_3, hyperchloremia, and an increase in H ion concentration. Clinical conditions warranting the use of Diamox or NH_4Cl are frequently associated with abnormal kidney function. Even slight renal impairment may serve to augment these deleterious effects on urinary and plasma HCO_3 levels.

The uncontrolled use of diuretics in toxemia of pregnancy may be hazardous to the expectant mother as well as to the fetus.[39] Goodlin and Kaiser[40] administered 6 grams of NH_4Cl daily to a patient group in the thirty-ninth and fortieth week of gestation. These workers observed an acidemia in both the mothers and the infants at term. The average blood pH of the newborns and the mothers demonstrated that the acidosis was more pronounced in the infants. It appears likely that the administration of NH_4Cl superimposes a metabolic acidosis upon an already unstable acid-base equilibrium in the newborn. Weisbrot and coworkers[41] found that 21 normal infants at birth exhibited an average pH of 7.21 with low circulating levels of HCO_3 and dissolved CO_2. Therefore, the total blood buffering capacity of the newborn is significantly reduced the first 24 hours of life. A slight uncompensated metabolic acidosis was found to exist in a large number of premature infants, by Reardon and associates.[42] Since any induced acidosis may contribute additional stress upon the newborn, diuretics should be administered with caution during pregnancy. The danger of subjecting the fetus to elevated H ion concentrations is exemplified by the high fetal mortality rate in mothers sufferings from diabetic acidosis.

In cases of cardiac insufficiency edema is frequently reduced by Diamox or NH_4Cl therapy. By the administration of 60 grams of NH_4Cl over a 5-day period, Sleisenger and Freedberg[43] produced a frank metabolic acidosis in patients suffering from congestive failure. These workers suggest that the altered renal circulation associated with cardiac insufficiency may significantly contribute to the hyperchloremia and excessive HCO_3 loss. Therefore, in cardiac patients it may be possible to therapeutically induce a

metabolic acidosis upon a pre-existent respiratory acidosis. Fordham and Relman[44] report a fatal case of cardiac failure that may be best explained on the basis of NH_4Cl intoxication. Only early recognition of this type of acid-base imbalance makes possible a prompt correction through the use of alkalinizing solutions.

Cardiotoxic states • In the cardiac patient an acidosis may produce serious and often lethal clinical manifestations.[45] In over 100 patients with severe hyperkalemia, multiple Stokes-Adams attacks, or cardiac arrest, Bellet and Wassermann[46] demonstrated the effectiveness of treatment with sodium lactate. This alkalinizing solution was life saving after more commonly used drugs and technics failed to restore cardiac rhythm. Bellet and coworkers[47] suggest that reversal of cardiotoxicity with sodium lactate is related to the alleviation of acidosis, a reduction in serum potassium, and utilization of lactate by cardiac muscle. These investigators[48,49] were able to show that the use of sodium lactate in cardiotoxic states had distinct advantages over $NaHCO_3$ or NaCl. While in general the results obtained with $NaHCO_3$ simulated those produced by lactate, the effects were less marked and of shorter duration. NaCl proved to be even less effective than the $NaHCO_3$ The use of this salt may only serve to aggravate the acidosis and hyperkalemia by increasing the amounts of circulating Cl ion.

Sodium lactate solutions have also been found by Weil[50] to influence the vasopressor response in individuals suffering from bacteremic shock and acidosis. Although this patient group received large doses of vasopressor agents the mean arterial blood pressure remained dangerously low. The administration of sodium lactate not only raised the average blood pH from 7.06 to 7.51, but also caused blood pressures to return to normal. During and after the use of this alkalinizing solution it was possible to decrease or discontinue vasopressants.

Diarrhea • The large losses of Na, K, Cl, and HCO_3 in cases of severe diarrhea may often lead to acidemic states. Although the total acid-base electrolytes are somewhat reduced, Gamble[51] points out that serum HCO_3 levels are decreased by as much as 50 per cent. Darrow[52] has found that diarrhea in infants can account for fluid losses up to 125 ml. per kilogram of body weight. This represents nearly half of the extracellular fluid volume. The alkali deficit accompanying fluid losses of this magnitude produces a metabolic acidosis. This has been substantiated by Winters and coworkers[53] who found an average blood pH of 7.22 in a group of 22 infants suffering from diarrhea.

The acid-base status,[54] the concentration of serum electrolytes,[55] the degree of hydration,[56,57] as well as the possibility of shock[58] are important factors in the determination of the fluid therapy regimen. Cheek[59] has attempted to correct diarrheal acidosis solely through the use of NaCl solutions. This worker concludes that if an early response is not obtained the continued administration of NaCl fails to restore either hydration or acid-base balance. A mixture of 3 parts saline to 1 part sodium lactate has been recommended by Hoffman[60] as the repair solution of choice. However, the use of this alkalinizing agent is not always successful because of the infants' inability to metabolize lactate. Following lactate administration Natelson and Barbour[61] found that large amounts of the unchanged substance was usually excreted by young children. Therefore, replacement of the theoretic HCO_3 deficit in pediatric patients may require 20 per cent more lactate than could be predicted on the basis of the Henderson-Hasselbalch equation. In these instances $NaHCO_3$ may be therapeutically more effective.

Assessment of bicarbonate deficit in terms of correctional therapy

Proper clinical management in extreme states of metabolic acidosis requires a prompt recognition of the HCO_3 deficiency. However, until the concentration of dissolved CO_2 has been clearly defined the lack of circulating HCO_3 cannot be established. The need for alkali is not entirely dependent upon serum HCO_3 levels but is directly related to the HCO_3/CO_2 ratio. This ratio is equal to approximately 20 at a blood pH of 7.40. According to the Henderson-Hasselbalch equation this requirement may be fulfilled when the HCO_3/CO_2 ratio is 40:2 or also at a variety of HCO_3 and dissolved CO_2 concentrations. In metabolic acidosis this ratio may fall far below 20 when a low serum HCO_3 is accompanied by a normal amount of dissolved CO_2. It is only possible to compute the amount of alkali necessary to bring such a ratio to 20 when the serum HCO_3 and dissolved CO_2 levels are known.

Using Table II it can be seen that a patient with a serum HCO_3 of 15 mEq./L. and a blood pH of 7.10 has a dissolved CO_2 of 1.5 mEq./L. These values correspond in Table III to a state of pure metabolic acidosis. The amount of alkali necessary to bring the HCO_3/CO_2 ratio to 20 may then be calculated as follows:

$$20 = \frac{HCO_3}{CO_2}$$

$$20 = \frac{15 + HCO_3 \text{ deficit}}{1.5}$$

$$HCO_3 \text{ deficit} = 20\ (1.5) - 15$$

$$HCO_3 \text{ deficit} = 15 \text{ mEq./L.}$$

To eliminate the necessity for carrying out this type of computation, Table IV has been prepared. The $NaHCO_3$ need expressed in terms of milliequivalents per liter of extracellular fluid has been calculated, using dissolved CO_2 levels of 0.5 to 7.0 mEq./L. at serum HCO_3 concentrations ranging from 5 to 50 mEq./L. The alkali deficit can be converted into grams of $NaHCO_3$ by multiplying by .084, or into milliliters of M/6 sodium lactate by multiplying by 6. Therefore, a HCO_3 deficiency of 15 mEq./L. requires 1.26 grams of $NaHCO_3$ or 90 ml. of M/6 sodium lactate per liter of extracellular fluid to bring the blood pH to 7.40. Assuming that 20 per cent of the body weight of an adult is extracellular fluid,

TABLE IV—ALKALI DEFICITS AT VARIOUS SERUM BICARBONATE AND DISSOLVED CARBON DIOXIDE CONCENTRATIONS*

	5	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**
0.5	5	4	3	2	1																																								
0.6	7	6	5	4	3	2	1																																							
0.7	9	8	7	6	5	4	3	2	1																																					
0.8	11	10	9	8	7	6	5	4	3	2	1																																			
0.9	13	12	11	10	9	8	7	6	5	4	3	2	1																																	
1.0	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																															
1.1	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																													
1.2	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																											
1.3	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																									
1.4	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																							
1.5	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																					
1.6	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																			
1.7	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1																	
1.8	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1															
1.9	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1													
2.0	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1											
2.1	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1									
2.2	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1							
2.3	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1					
2.4	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1			
2.5	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1	
2.6	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4	3	2
2.7	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6	5	4
2.8	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8	7	6
2.9	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10	9	8
3.0	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12	11	10
3.1	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12
3.2	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16	15	14
3.3	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	16
3.4	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18
3.5	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20
3.6	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24	23	22
3.7	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26	25	24
3.8	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28	27	26
3.9	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30	29	28
4.0	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32	31	30
4.1	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34	33	32
4.2	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36	35	34
4.3	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38	37	36
4.4	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40	39	38
4.5	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42	41	40
4.6	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44	43	42
4.7	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46	45	44
4.8	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48	47	46
4.9	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50	49	48
5.0	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52	51	50
5.1	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54	53	52
5.2	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56	55	54
5.3	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58	57	56
5.4	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60	59	58
5.5	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62	61	60
5.6	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64	63	62
5.7	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66	65	64
5.8	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66
5.9	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68
6.0	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72	71	70
6.1	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74	73	72
6.2	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76	75	74
6.3	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78	77	76
6.4	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80	79	78
6.5	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82	81	80
6.6	127	126	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83	82
6.7	129	128	127	126	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84
6.8	131	130	129	128	127	126	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88	87	86
6.9	133	132	131	130	129	128	127	126	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90	89	88
7.0	135	134	133	132	131	130	129	128	127	126	125	124	123	122	121	120	119	118	117	116	115	114	113	112	111	110	109	108	107	106	105	104	103	102	101	100	99	98	97	96	95	94	93	92	91	90

*Serum bicarbonate (mEq./L.) is shown in boldface figures at top of table; dissolved carbon dioxide (mEq./L.) is shown in italics; and alkali deficits are shown in lightface figures.

therapeutic doses can be quickly determined.[62]. If the above patient weighed 50 kg., the extracellular volume would be considered 10 liters. Therefore, 12.6 grams of $NaHCO_3$ or 900 ml. of M/6 sodium lactate are theoretically required to bring the pH to 7.40.

The administration of repair solutions of this type should always be accompanied by serial serum HCO_3 and blood pH determinations. A critical evaluation of the recovery period is, furthermore, made possible when these values are used in conjunction with the serum HCO_3 and pH table. In addition, such an analytic technic minimizes the danger of an induced alkalosis.

Summary

Metabolic acidosis has been shown to be a lethal complication in a variety of clinical states. Early recognition of this condition may be a vital factor contributing to a better prognosis. Serum HCO_3 or blood pH determinations alone have been found to be incomplete diagnostic tools for the assessment of metabolic acidosis or of any other type of acid-base imbalance. Establishment of the type and degree of an acidosis or alkalosis requires solution of the Henderson-Hasselbalch equation, which contains three variables: pH, serum HCO_3, and dissolved CO_2. Simple technics for laboratory analysis of blood pH and serum HCO_3 have been presented. These values may be applied to Table II in order to determine the level of circulating dissolved CO_2, thereby circumventing the rigorous mathematics inherent in solving the Henderson-Hasselbalch equation.

It has been demonstrated that knowledge of the ratio of HCO_3/CO_2 is essential for a quantitative estimation of the theoretic alkali deficit. In metabolic acidosis this ratio often falls far below the normal value of 20 because of losses of base and fluctuations in the dissolved CO_2. The need for calculating this ratio prior to establishing the $NaHCO_3$ deficiency has been eliminated by construction of Table IV. This provides an accurate means for rapidly estimating the amounts of $NaHCO_3$ theoretically required to bring a variety of serum HCO_3 and dissolved CO_2 ratios to 20. A method has been proposed for converting the lack of base into therapeutic dosages of M/6 sodium lactate as well as $NaHCO_3$. A sound rationale is thus provided for the use of alkalinizing repair solutions after a critical evaluation of metabolic acidosis has been made. *1721 Griffin Ave.*

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Postoperative urinary retention*

ADDISON HOMBS, D.O., Associate Professor of Surgery, Kirksville College of Osteopathy and Surgery, Kirksville, Missouri

Tradition plays a continuing role in patient care regardless of our enlightened scientific accomplishments. Just as we continue to adorn our surgical patients with bed socks for no known reason, other than "it has always been done that way," we are also taught to catheterize the postoperative patient in routine fashion. Preceptors continue to pass this advice down to their students, who too often absorb their training in a parrot-like manner, and the evil is perpetuated from one generation to the next. The catheter is an extremely effective instrument when properly used by qualified personnel, but it can be extremely dangerous when promiscuously used by individuals untrained and unappreciative of the potentially lethal weapon they hold in their hand.

It is not my intention to ridicule or cast doubt on established facts concerning urinary retention in the postoperative patient. It is acknowledged that overdistention of the bladder and residual urine produce an excellent medium for urinary tract infection. However, the inflexible routine of postoperative care practiced by many surgeons may be responsible for the production of urinary tract infections. The patient must still be treated as an individual and not as a machine, equipped and timed to function in the identical manner of his prototype.

In most institutions, the mechanical chore of catheterization continues to be delegated to those least qualified to perform it. Consequently it is usually considered a menial task, and is performed in a hasty, inept manner, with little consideration for the patient, and done only for the purpose of fulfilling an order and completing a chart. While carrying out this routine and objectionable duty as a trainee, it became increasingly apparent to me that only a small amount of highly concentrated urine was being obtained on catheterization, and that in many instances a catheterization cycle was established, necessitating repeated instrumentation on certain individuals for one or several days postoperatively. This was associated with the usual side effects of multiple catheterization: urethritis, cystitis, bleeding, discomfort, and associated patient resentment.

After entering my own surgical practice, I determined to investigate this problem, utilizing my own patients as controls against patients of other surgeons who practiced routine postoperative catheterization. For this purpose a total of 8,674 general surgical cases were reviewed, covering a period from 1946 to 1959. No urologic cases were reviewed, and cases in which an indwelling catheter was employed in postoperative care were excluded. Surgical procedures were categorized according to body regions and areas, that is, high and low abdominal, pelvic, head and neck, orthopedic, and so forth. Anesthetic types

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were considered, but it was my impression that there was little relationship between anesthesia and postoperative retention. Operative time was considered but apparently was not contributory. Preoperative urinalyses were evaluated in all cases for evidence of uropathy. In the control cases, constituting 1,969 of the total, the first postoperative specimen of urine was sent to the laboratory for routine examination for a period of 3 years. Since these urinalyses failed to produce conclusive findings, this routine was abandoned.

Because of charting inadequacies by nursing personnel, catheterization was recorded in many instances without record of volume. In many charts, postoperative urinary tract disorders had to be assumed from nurses' records which indicated dysuria, frequency, and urgency, and from temperature curves suggestive of involvement. In repeated instances, medications had been prescribed which would properly treat urinary tract infection, but progress notes failed to rationalize the orders. Many patients were receiving antibiotic therapy for other surgical and medical problems, and this fact alters the true evaluation. However, in spite of the recognized inaccuracies of this survey, certain patterns and observations seem worthy of mention.

Analysis of averages of figures compiled indicated that approximately 28 per cent of all patients with routine catheterization orders were catheterized in the first 12-hour postoperative period. Of these patients, 48 per cent had a single catheterization, 36 per cent had two catheterizations, 11 per cent had three catheterizations, and 5 per cent underwent four or more catheterizations in the postoperative period. Sixteen per cent of all patients catheterized developed actual or suggested uropathy such as urethritis, cystitis, or pyelitis. Urine volume varied from none obtained, to 1,700 cc. with an average of 120 cc. or approximately 4 ounces of urine. In the control cases, 6 per cent of cases required catheterization, based on the criteria of a palpable full bladder and lack of adequate sphincteric control necessary to initiate a urinary stream after all usual conservative measures had failed. Female patients who had undergone pelvic operations and patients having operations for herniated intervertebral disk were particularly likely to require catheterization. It was interesting to note that patients having special duty nursing service were more likely to need catheterization than those under general ward care. Patients who were nurses or allied medical personnel seemed to require catheterization more often than other occupational groups, suggesting a psychogenic factor. These observations and the following related anatomic, physiologic, pharmacologic, and psychic factors form the basis of this paper.

Anatomically, the bladder represents the collecting organ of the urinary tract, and its capacity varies from 200 to 500 cc. in the average adult patient. The efferent nerve supply is derived from visceral branches of the second, third, and fourth sacral autonomic nerves and the lumbar sympathetics. The afferent fibers travel along the sympathetic chain to the posterior roots of the first and second lumbar nerves and the sacral autonomic nerves, into the sacral posterior nerve roots. The detrusor musculature of the bladder maintains a constant tonus with a pressure of from 6 to 10 cc. of water until a considerable quantity of urine is collected.[1] When bladder volume increases the intravesical pressure to from 18 to 30 cc. of water, the desire to void becomes evident. The proprioceptive impulses from the bladder are carried to the sensory cortex, and under favorable conditions the detrusor contracts, the internal sphincter of the bladder relaxes, the external sphincter responds, and the bladder empties. However, the average bladder capacity is an individual matter, subject to habit, demand, psychic stimulus, medications, and so forth.[1-3] These factors enter into the physiologic necessity for micturition, and play an important part in postoperative urinary functions.

In the postoperative patient, there has been an assumption that bladder activity should closely parallel or equal that of the normal, active, and healthy individual. Little reasoning has been applied to the physiologic and psychic alterations that take place in the average general surgical patient, and in consequence, the catheter is employed with gross disregard to his response. It has been suggested that postoperative urinary retention is caused by temporary decompensation or atonicity of the bladder, a mechanical condition resulting from overdilation of the bladder for a long period, and is probably the indirect result of oversedation of the patient in the preoperative phase.[4]

This may well be true, but it scarcely rationalizes the order for routine catheterization in 8 to 12 hours after surgery, if the patient does not void. Too often, this urethral insult is productive of from 50 to 150 cc. of highly concentrated urine, which seems a minimal amount to represent a distended bladder and necessitate catheterization as a routine.

Observing a few of the many factors associated with surgical therapy makes the reasons for this low urinary volume more recognizable. Moyer[5] states, "If after the infliction of pain, water is drunk or is injected intravenously as five per cent glucose in water, it is largely retained, the rate of urine flow remains low, and its specific gravity remains high, even though dangerous excesses of water may be incurred." The administration of narcotics for the control of pain further reduces the volume secretion of urine, since morphine diminishes urinary response to water administration, both by diaphoresis and liberation of the antidiuretic hormone of the pituitary.[2,6] Thus we create pain by surgical intervention, and in employing pain relief measures, we further embarrass the secretory volume of the kidney.

A further examination of the psychophysiologic response is indicated for additional rationalization. Irrespective of emotional stability, the average patient approaches surgery with fear and trepidation. In the hospitalization of the patient, new experiences, happenstance, and routines combine to produce an emotional diuresis, resulting in frequent and often copious passage of urine, usually of a low specific gravity. Diaphoresis and increased metabolic response to this psychic trauma serves to further de-

plete the fluid reserves of the body, producing a state of relative dehydration and hemoconcentration. Oral fluid intake is denied the patient after late hours of the preoperative day. Preoperative narcotics and medications are administered, which further reduce renal secretion. The patient is instructed to void, or is catheterized, in the immediate preoperative preparation and in many instances the catheter is left indwelling for continuous drainage during the surgical procedure. The environment of the operating room usually produces thermal changes above those normally experienced by the patient, and an array of heavy surgical drapes and blankets contribute to excessive fluid loss from sweating. Insensible fluid loss during anesthetic administration must be considered. Blood and serum loss during the operative procedure may be excessive and must be included in the total fluid depletion. In the presence of hypotension or true shock during the operative procedure or in the immediate postoperative phase, stress vasoconstriction, as an adrenal response, further reduces renal blood flow with an associated diminution of urine volume. Even though fluids are administered during and after surgery, it is not difficult to visualize their fate as they are distributed to thirsty dehydrated tissues and to restoration of circulatory volume, or are arrested in the glomerular filtrate by physiologic response to pain and pharmaceuticals.

In the early postoperative period the patient is continually bombarded with suggestion from nursing personnel, interns, and other anxious attendants relative to his desire to empty his bladder. This repeated suggestion confounds the psyche until the patient becomes convinced that he does have a full bladder, and that he must void, if for no other reason than to satisfy the anxiety of medical personnel. This physiologic maneuver is usually attempted first with the patient in a fully recumbent position, or propped precariously on a bedpan, which is anatomically incorrect from the outset, since visceral pressure is an integral physiologic aid to micturition. This failing, the patient is helped to stand at the bedside and with the watchful assistance of attendants, he is expected to perform a natural function which from early childhood training to adulthood he has been taught to perform in absolute privacy in deference to modesty and social custom. Bladder volume being minimal, and voluntary sphincteric action unpredictable during this early postoperative phase, the patient fails to void in quantity sufficient to satisfy his critics, and since the magic time of 8 to 12 hours has passed since surgery, the catheter sequence is initiated. This serves to institute additional physiologic and psychic phenomena. Hix and associates[7] have demonstrated vasoconstriction and lowered renal circulation with attendant diminution of renal function when ureterorenal reflexes are initiated by instrumentation. Hix[8] postulates that nerve supply to the ureters and bladder trigone is essentially the same based on the law of bilateral symmetry, and as such, irritation of the trigone and urethra by catheter would produce diminution of renal function in the same manner as the ureterorenal reflex, thus lowering urinary output.

The patient has usually been preindoctrinated by relatives and friends to dread possible catheterization during this postsurgical experience. When the anticipated instrumentation develops, a feeling of frustration and anxiety ensues which may render voluntary micturition impossible as the next scientifically calculated period for his bladder to be full approaches. Catheterization becomes repetitious, demanding that the patient increase his urinary output while normalizing surgically insulted physiology, educate himself to rapid sphincteric control, and overcome his sense of modesty—all of this in a mad race with a dogmatic routine that states that his bladder must be full in 8 to 12 hours. With this well-meaning but poorly rationalized routine, the many complications of the urinary tract are spawned, producing a justifiable condemnation of the general surgeon by our urologist brethren. To be sure, an overly distended bladder may lead to atonicity and ureterorenal reflux, but normotonus prevails and the usual caliber of the ureter and bladder will be restored soon after the bladder is empty.[2] On the other hand, catheterization, benign as it has been made to appear, is a marked etiologic factor in the development of acute urinary tract infections. These eventually become the crippling pyelonephritis and resistant infections that we are daily called upon to treat. Regardless of the caution utilized in sterile catheterization technic, recent research has shown urinary tract infection from autoinoculation from the urethra to be a prime factor in production of chronic pyelonephritis.[9] With this in mind, can we afford to overlook the individuality of the patient for the concept of routine?

It is therefore necessary to approach the patient as an individual, evaluating his urinary retention from an individual standpoint, and placing the decision for catheterization in the hands of a responsible observant physician, rather than at the discretion of a busy intern, an untrained orderly or hospital aide, or the charge nurse with her indoctrination in ritual and routine. For that reason, the following program has been evolved for my general surgical patients:

1. No orders are written for routine catheterization.
2. Nurses, clinical clerks, interns, and other hospital personnel are forbidden to suggest to the patient that they might need to void. Most patients will convey this desire when they become uncomfortable.
3. Prostigmin or Urecholine is utilized in small dosages to stimulate the smooth muscles of the urinary bladder.
4. Careful palpation of the lower abdomen is instituted in the early postoperative period to determine the presence of a distended bladder, should the patient complain of pain.
5. If the patient has a distended bladder and cannot void, psychosuggestion with a placebo injection and the strong inference that "This shot will do the job within 5 minutes," has been extremely effective. Sympathetic encouragement to the distressed patient is frequently rewarding, but the threat of catheterization is never used.
6. As a final effort, catheterization under rigid sterile technic with recatheterization guided only by patient need or demand.
7. Patients who do require catheterization are ob-

served closely for urinary tract infection and treated positively at first complaint.

Summary

A series of 8,674 general surgical cases was reviewed, showing an incidence of 28 per cent catheterization in routinely catheterized patients, and 6 per cent in control cases catheterized on demand. Approximately 16 per cent of all catheterized patients developed proved or suggestive urinary tract infections and irritations.

No rationale for routine catheterization orders could be determined since urinary bladder response is an individual reaction based on physiologic, pharmacologic, psychic, and other factors. Routine catheterization presents the possibility of compounding surgical problems with crippling, debilitating urinary tract disease.

A program for evaluation and management of the urinary bladder in the surgical patient has been presented. Surgeons are urged to consider each patient as an individual rather than as a stereotyped clinical entity.

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The venous phase of cerebral angiography*

JOHN J. GILLIGAN, D.O., Warrensville Heights, Ohio

"Arteries and veins do not run together in the brain as in other parts of the body."[1]

Introduction

Cerebral angiography has become an important diagnostic procedure in many institutions in this country, largely through studies cooperated in by neurosurgeons, anesthestists, and radiologists. Although admittedly our knowledge is still incomplete, advances have been made, as evidenced by the recent literature. Most of the publications have dealt with cerebral arteriography; only lately have articles concerning the venous phase of cerebral angiography appeared in American publications. European investigators apparently were first to recognize the value of the cerebral phlebogram. Egas Moniz, about 4 years after his introduction of cerebral arteriography,[2,3] became the first person to obtain a cerebral phlebogram.[4] Like many such discoveries this one was accidental, having resulted from erroneous timing of an exposure on a carotid arteriogram. Egas Moniz, quick to recognize the potential value of the discovery, modified his technic of carotid arteriography to include this phase of cerebral circulation.

The purpose of this paper is to review the literature dealing with the venous phase of cerebral angiography, and to correlate and analyze material accumulated between January 1952 and April 1958 at the Hospitals of the Philadelphia College of Osteopathy.

Several of the earlier investigators expressed doubt that the central veins and deep dural sinuses of the brain are of any real importance diagnostically. Their opinions were based on the variability of the position of these structures and on the frequent unsatisfactory visualization attained on angiograms. In recent years, however, Johanson[5] and Ecker[6] and Wor-

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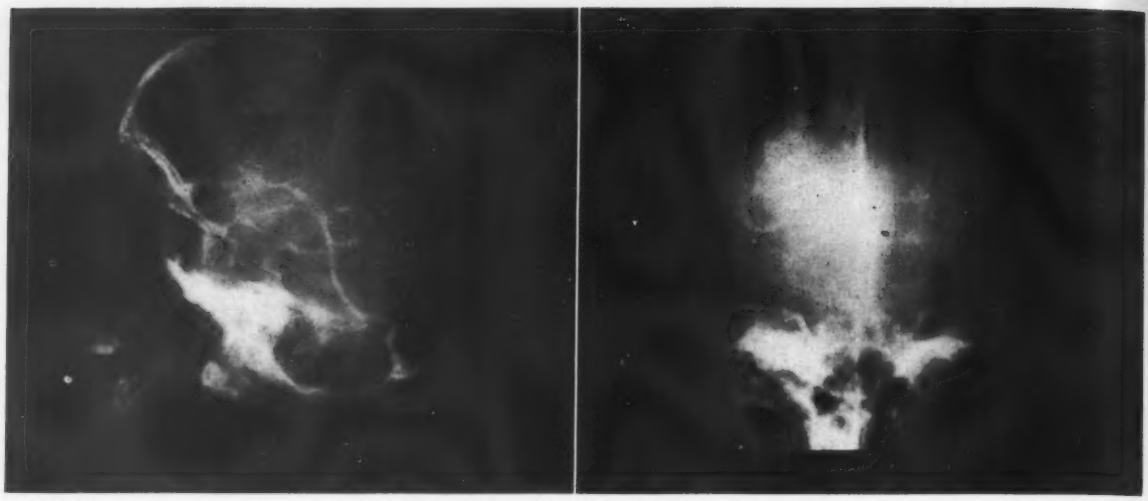

Fig. 1. Venous phase of cerebral angiogram in normal patient demonstrating excellent visualization.

inger,[7] Laine,[8] Wolf,[9] and Mokrohisky[10] and their associates have found the deep central veins and dural sinuses to be of specific diagnostic value in many instances. These investigators believe that these structures are relatively constant in position, and that they are usually well visualized with present-day contrast media and technics.

Gvozdanović[11] and Lorenz[12] appear to be the only investigators who have investigated to any extent the superficial cerebral veins, or attached any diagnostic significance to them.

Direct opacification of the venous system of the brain was carried out by Fischgold and his coworkers[13] by various methods, including injection of opaque media into the sinuses, the ophthalmic vein and the diploe of the skull. They established that the blood supply to the brain was through the carotid and vertebral arteries alone, as all the medium injected into the venous system was carried away from the brain. Little additional information was gained by these methods, which were considered too dangerous for practical use.

Embryologic basis

In a fetus of 3 months, a double system of cortical veins exists.[14] The central cortex is drained caudally through a group of sylvian veins, and from there through the region of the basal ganglia. The superficial veins and parts of the hemispheres are drained through the dural sinuses. At this stage these two systems are distinct and separate and they do not anastomose. In the older fetus this duality changes, and all parts of the brain are drained by both systems. This is in preparation for extrauterine existence, when there is a well-developed anastomosis between the deep and superficial veins. There is apparent correlation between the number, caliber, and position of the veins, and the areas that they drain. The veins draining the higher functional centers are more numerous, larger in caliber, and more constant in position and anastomosis.

Anatomic structures • The superficial cerebral veins drain the convexity of the hemispheres in the direction of the superior sagittal, transverse, and cavernous sinuses. These superficial veins can be grouped in three general classifications.

The ascending veins pass superiorly and posteriorly, and then curve rather sharply forward just before they enter the superior sagittal sinus. The forward curve of these veins is not as marked in the frontal region as it is in the parietal and occipital regions. These veins therefore enter the superior sagittal sinus against the blood flow. The largest vein in this group is the ascending vein of Trolard.

The descending veins pass interiorly and posteriorly and terminate in the lateral sinus. The most prominent vessel in this group is the vein of Labbé, which joins with the vein of Trolard to form an important radiographic landmark which Moniz called "the venous crossroads of the brain." This landmark is opposite the island of Reil.

The third group empties into the cavernous sinus. The major vein is called the superficial middle cerebral vein. It connects the "venous crossroads" with the anterior portion of the veins of the sylvian fissure.

Physiologic and pathologic function • The superficial veins have no valves; therefore they may be considered functionally as a single unit. With the introduction of an intracranial pathologic process, expanding or thrombotic in nature, one can expect certain changes in the superficial system. The direction of venous drainage may change, or the drainage may become limited to one direction. The luminal caliber of the veins of Labbé or Trolard may be increased as a result of the change in direction of drainage. These thin-walled veins may be pressed against the inner table of the skull so that they cannot fill. The anatomic position of these veins is usually not altered.

In a series of 500 cases Gvozdanović[11] drew the following conclusions: Deficient filling of the superficial veins may be due to (1) slowing down or in-

terruption of circulation resulting from compression or thrombosis, (2) a combination of compression and thrombosis, or (3) flattening of the gyri due to cerebral edema. Lack of filling of the superficial veins may be due to (1) the size of the region involved, (2) the change in direction of drainage, or (3) a superficial marginal vein is seen about the periphery of a tumor that has no typical vascularity.

It has been noted that in some cases of subdural hematoma the superficial veins are pushed away from the inner table of the skull. This is often better demonstrated in the anteroposterior view of the phlebogram than it is in the arterial phase.

Deep veins and dural sinuses

The physiology of cerebral circulation is not fully understood. It is influenced by local, systemic, and technical factors. The anatomy of the deep and superficial cerebral veins is relatively constant, but anatomic variations are numerous

Gross and radiographic anatomy[1,6,10,15,16] • The internal cerebral vein is located along the upper limits of the roof of the third ventricle. It is paired and symmetrical. The course of this vein is between the posterior portion of the corpus callosum and pineal body. Behind the splenium the paired branches join to form the great vein of Galen. The internal cerebral vein drains the white matter near the vein's origin, portions of the basal ganglia, parts of the choroid plexus of the third and lateral ventricles, and the thalamus. Roentgenographically this vein is most easily recognized in the lateral projection. It describes a gentle curve; anteriorly it is concave downward and posteriorly it is concave upward. In the anteroposterior view it appears foreshortened and situated slightly lateral to the midline. Because of its curve its anterior end is closer to the midline than its posterior aspect.

The great vein of Galen is, as previously mentioned, formed by the two branches of the internal cerebral vein which join in the midline behind the splenium of the corpus callosum. The vein gradually increases in size as it is joined by other tributaries It curves upward around the splenium and enters the inferior sagittal sinus at a right or slightly obtuse angle. In the phlebogram this vein is also best recognized in the lateral projection. It is seen as a direct continuation of the internal cerebral veins and no abrupt change in luminal caliber can be detected at its origin. In curving around the splenium it forms a half- or three-quarter circle. In the anteroposterior projection it is viewed as an increased radiodensity in the midline superimposed on the superior and inferior sagittal sinuses.

The inferior sagittal sinus is located in the posterior two thirds of the free margin of the falx cerebri. The anterior portion of this sinus is closer to the inner table of the skull than is the posterior portion. The luminal caliber of the inferior sagittal sinus is greater posteriorly than it is anteriorly. It is directly continuous with the straight sinus and is best seen in the lateral projection. The vessel is concave downward and convex upward, although variations do occur and at times it is seen as being practically straight. In the anteroposterior view this sinus is located in the midline superimposed on the superior sagittal sinus.

The straight sinus is a direct continuation of the inferior sagittal sinus. It begins at the anterior margin of the tentorium cerebelli at the junction of the inferior sagittal sinus and the great vein of Galen. It courses posteriorly along the junction of the falx cerebri and tentorium cerebelli. It is usually straight, but it may curve gently upward or downward. The straight sinus is triangular in cross section. It empties into the confluence of sinuses or into either lateral sinus, most frequently the left. In the lateral phlebogram this sinus is usually well demonstrated because of its large luminal caliber. In the anteroposterior position it is located in the midline in an inferior position.

The striothalamic vein runs in an anteromedial and oblique direction in a groove between the caudate nucleus and the thalamus in the floor of the lateral ventricle. Anteriorly it turns downward and medially through the posterior portion of the interventricular canal, where it joins the internal cerebral vein. It receives small branches from the anterior and middle portions of the lateral wall of the ventricle. In the lateral phlebogram this vein and the internal cerebral vein form a curve convex anteriorly. There are many variations to the shape and acuity of this angle. Moniz has called this "the venous angle of the brain." In the anteroposterior projection the striothalamic vein runs downward and medially to join the internal cerebral vein.

The vein of the septum pellucidum courses from the lateral portion of the anterior horn medially and posteriorly along the wall of the septum immediately beside the midline. Here it usually joins the anterior portion of the internal cerebral vein, but occasionally it empties into the striothalamic vein. In the lateral view this vein is usually recognized by its somewhat wavy appearance, although in certain cases it is straight. It is smaller in luminal caliber than the internal cerebral vein. Roughly it parallels the floor of the anterior cranial fossa. It is not always well visualized at angiography. When it is visualized, it is easily recognized in the anteroposterior view. Its course is medially and obliquely toward the midline; then it swings somewhat laterally again to terminate in the internal cerebral vein.

The vein of the posterior horn courses the medial wall of the posterior horn of the lateral ventricle.

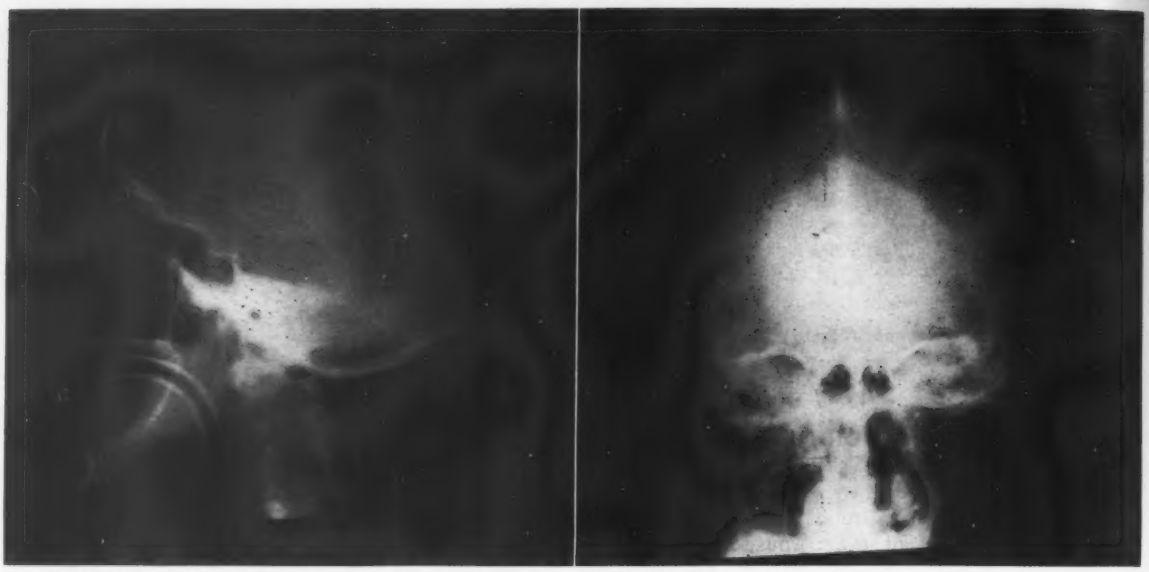

Fig. 2. Good visualization of the venous phase in a patient with a primary brain tumor (right meningioma).

This vein is formed by smaller veins draining the trigone and lateral wall of the ventricle. It empties into the internal cerebral vein at the latter's posterior aspect. When visualized, this vein is usually seen in the lateral projection, and it is located slightly above the internal cerebral vein. Its course is sinuous. In the anteroposterior view it runs parallel to and below the striothalamic vein.

The choroidal vein arises from the choroid plexus of the lateral ventricle. It pursues a sinuous spiral course anteriorly, and empties into the internal cerebral vein or the striothalamic vein at about the level of the interventricular canal. This vein when visualized is seen only on the lateral projection. It is easily recognized by its spiral course. It is located slightly above the internal cerebral vein.

The basilar vein of Rosenthal originates in the anterior perforated substance. It passes posteriorly along the optic tract and around the cerebral peduncles, and it empties into the great vein of Galen. The basilar vein receives several small tributaries along its course. On the phlebogram in the lateral view this vein is recognized by the stellate appearance of the small veins forming its origin, which is about 1 cm. above the sella turcica. It runs posteriorly for a few centimeters above the uncus, then turns upward to join the great vein of Galen. In the anteroposterior view it originates laterally and takes a zigzag course upward and medially to the midline where it joins the great vein of Galen.

In the interest of completeness, several of the smaller veins of the brain that are not consistently visualized on the phlebogram should be mentioned. The occipital vein is probably the most consistently visualized of these veins. It drains the inferior medial surface of the occipital lobe and empties into the vein of Rosenthal or the great vein of Galen. The superior cerebellar veins drains blood from the superior part of the cerebellum and empty into the great vein of Galen. The anterior caudate vein parallels the septal vein but is seen at a higher level. It receives branches from the longitudinal caudate veins and the venous drainage of the white matter. The anterior caudate vein originates at the lateral border of the lateral ventricle between the upper portion of the caudate nucleus and the lower border of the corpus callosum. It ends in the striothalamic vein a few centimeters behind the interventricular canal.

The large dural sinuses that lie at the periphery of the brain are: the superior sagittal sinus, which usually can be visualized and which runs from the foramen cecum to the internal occipital protuberance; the transverse or lateral sinus, which communicates with the sigmoid sinus and jugular vein; and the superior petrosal sinus, which is seen anteriorly and posteriorly to the sella turcica. These sinuses, with the cavernous sinuses lateral to the sella turcica, make up the circular sinus.

Physiologic function[15,16,17] • The physiology of the cerebral circulation is far from being fully understood. Estimates of the average circulation time of blood through the brain vary in the reports published. Exactly what occurs at the blood-brain barrier when a radiopaque medium reaches it is still a moot question. Because of the circulatory dynamics of the brain, opaque media injected into the common carotid artery remain in the ipsilateral hemisphere, unless the blood supply to the opposite hemisphere is obstructed either by design or by a pathologic process. If the latter is the case, collateral circulation is then established through the circle of Willis. The vessels and sinuses located in the midline will be demonstrated regardless of the site of injection. The opacification of these midline structures will be diminished because of dilution of the medium by blood from the opposite side.

It is known that certain systemic and local phenomena cause changes in the cerebral circulatory

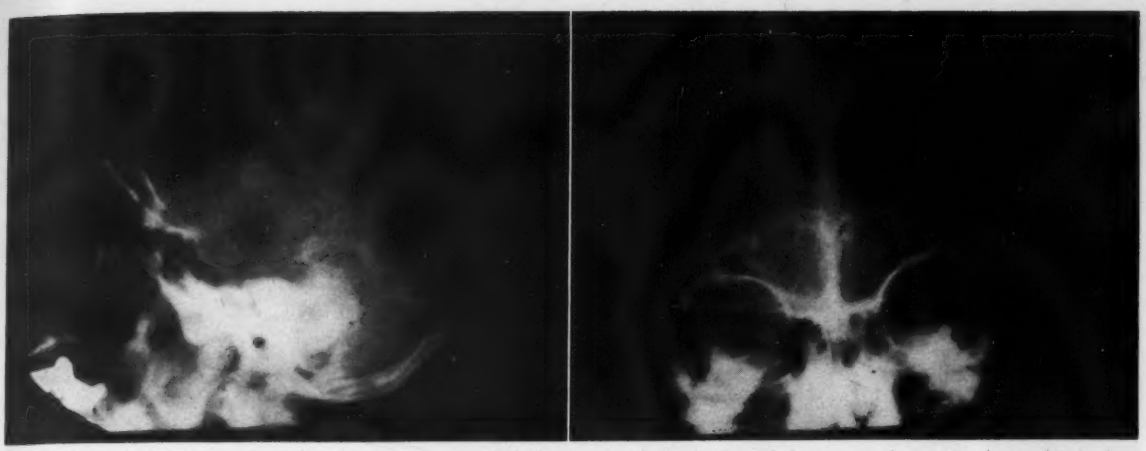

Fig. 3. One of the three cases of carotid aneurysm reported, showing good visualization of the venous phase. No abnormality is demonstrated.

mechanism. Systemic changes such as lowering of the blood pressure cause a slowing of cerebral circulation; increased carbon dioxide concentration in the brain speeds cerebral circulation. The chemical constituents of the blood have an effect on circulation time. Local changes such as cerebral edema slow the cerebral blood flow, and arteriovenous malformations speed circulation.

Considering these factors along with the technical aspects of performing a cerebral angiogram, one can easily appreciate the confusion about cerebral circulation. The technical problems involve (1) speed of injection, (2) needle placement in the artery, and (3) the effect of a foreign substance in living tissue. Automatic hydraulic injection apparatus standardizes injection speed, but to date such devices are not in wide use. Manual injection in experienced hands can be quite satisfactory. Competent needle placement depends largely on the experience of the operator. It would appear that little can be done about tissue reactions. Moniz, as quoted by Curtiz,[17] contended that the superficial cerebral veins would be visualized 2 seconds after carotid injection, and that the deep veins would be visualized in 4 seconds. He was also of the opinion that no contrast medium was visible in the brain after 6 seconds. Woringer and his associates[7] described the normal cerebral transit time as being between 7 and 10 seconds, and suggested that the normal arterial phase lasts from 2 to 3 seconds, the capillary phase from 1 to 2 seconds, and the venous phase from 3 to 6 seconds; circulation time greater than 10 seconds was considered abnormal. These periods were measured from the time opaque medium was seen in the carotid siphon until it appeared in the dural sinuses. In cases of tumor, Woringer found the circulation time increased 1 to 3 seconds over his established normal values, whether or not the tumor was visualized.

In similar observations cited by Woringer, Wickbom and Schurr considered normal cerebral circulation time from 6 to 10 seconds, Tonnis and Schiefer found 5 to 6 seconds to be average in their series of cases, and Sanchez-Perez recorded average circulation time as 4 to 5 seconds. Curtis,[17] on the other hand, has reported visible opaque medium in the dural sinuses as long as 12 seconds after carotid injection in apparently normal subjects. He also contends, contrary to Moniz and several other investigators, that the deep cerebral veins visualize before the superficial cerebral veins. From his observations he points out that the three phases, arterial, capillary, and venous, overlap considerably; in certain instances all phases are present at the same time.

These observations made by various investigators vary and conflict. This is not to say that their observations are invalid, for the variations are in all probability due to differences between individual technics. It therefore becomes apparent that an investigator utilizing a particular technic would do well to establish his own individual norms based on his experience and observations in his own series of cases.

Radiographic landmarks

In the evaluation of the venous system of the brain there are several important landmarks,[1,6,10,11] the most important and constant being probably "the venous angle of the brain," which locates the interventricular canal. The junction of the inferior sagittal sinus, straight sinus, and great vein of Galen marks a relatively rigid point at the anterior border of the tentorium cerebelli which is seldom influenced by intracranial pathology. This point can be considered as a pivot on which the septal vein, internal cerebral vein, and great vein of Galen may be displaced either upward, downward, laterally, or backwards. The inferior sagittal sinus is relatively fixed and it also is seldom displaced by tumors. The basilar vein of Rosenthal usually can be visualized. It parallels the anterior choroid artery, which is not frequently visualized and is the only artery that runs directly posterior from the carotid siphon outside of the arteries of the longitudinal fissure. Since it is not frequently visualized its value in angiography is limited. However, because the basilar vein of Rosen-

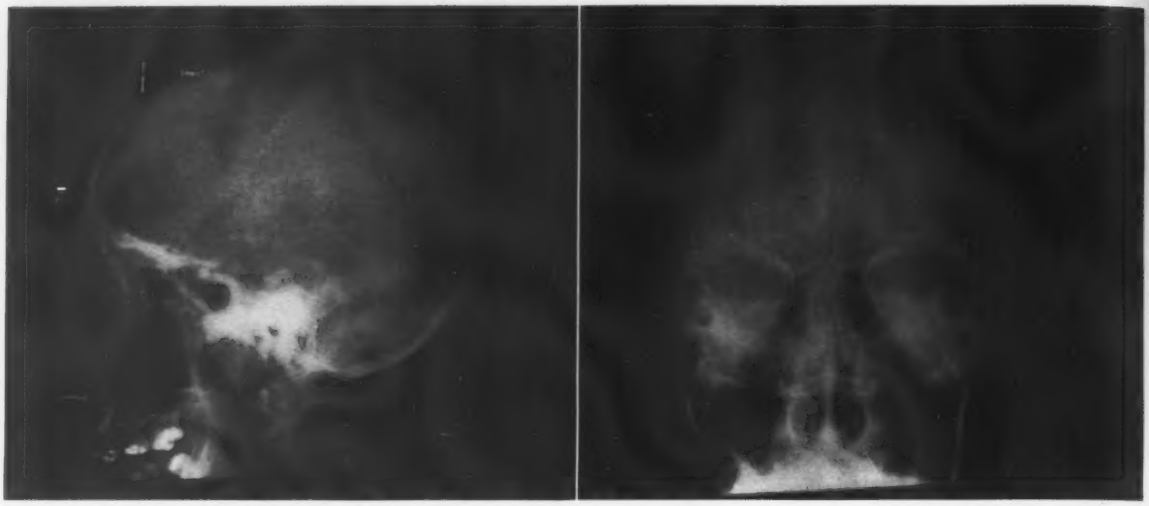

Fig. 4. Arterial spasm. In the lateral projection, note the opaque media in the internal carotid artery while at the same time many of the deep veins are also visualized.

thal parallels the anterior choroid artery, displacement of the basilar vein can be of diagnostic value in temporal lobe tumors when the anterior choroid artery is not seen. If tumors occur in this area without obvious displacement of the basilar vein, there may exist an arteriovenous shunt between the anterior choroid artery and this vein.

Generally speaking there are two types of displacement of the deep central veins. When the tumor lies in close proximity to the central veins and affects them by direct pressure, the displacement is considered to be localized; only portions of the deep central veins are displaced and distorted. When a tumor is at the periphery of the brain, displacement is said to be "en bloc," meaning that the entire deep central venous system from the anterior border of the tentorium forward is displaced as a unit.

As in the case of the arteries, not all the veins are visualized all the time. This will frequently cause confusion in locating important landmarks. There are several methods outlined by Mokrohisky[10] for determining the true "venous angle of the brain." The "false venous angle" can be recognized if: (1) the tributaries of the internal cerebral veins open into it at its most cephalic limit, (2) the tributaries show a gradual slope downward and backward and lack the smooth curve of the striothalamic vein, (3) the tributaries enter the internal cerebral vein at a right angle, or (4) the tributaries at the junction with the caudate vein are represented by a dense dot and lack the smooth curve of the striothalamic vein.

There have been many methods devised by investigators to locate and measure the position of the "venous angle." Johanson,[1] Wolf,[9] and Laine[8] have all devised methods using constant bony landmarks on the inner table of the skull. They have computed average distances from these bony landmarks for the location of the "venous angle." The investigators agree, however, that these methods are not completely reliable, and that observation and inspection of the deep cerebral veins are preferable.

Pathologic conditions

The basic findings in angiography have been widely applied in clinical studies.[1,5,8,9,10,13,15,18,19] It is possible that an intracranial lesion may affect both arterial and venous systems, or one and not the other. Vascular lesions are particularly amenable to angiographic study. Aneurysms are usually well demonstrated and localized on the arterial phase of the angiogram. Most aneurysms occur at the carotid siphon level, although they may occur anywhere in the vascular tree.

Arteriovenous malformations are due to the failure of the vascular wall to differentiate into artery or vein, as demonstrated by direct communication of afferent and efferent vessels. Although these malformation are usually developmental in origin, they may occur as a result of trauma, usually at the base of the brain. Such lesions occur at the carotid siphon as it passes through the cavernous sinus, and are demonstrated on the angiogram by the early visualization of the cavernous sinus with opaque medium. In this condition frequently large veins are seen to enter the orbit. Clinically this produces a pulsating exophthalmus. Vascular calcification is often associated with venous angioma.

In cases of symmetrical hydrocephalus, dilatation of the lateral and third ventricles can be caused by stenosis of the aqueduct of Sylvius or occlusion of the aqueduct by tumor. The angiographic appearance depends on the degree of dilatation. Minimal dilatation may or may not disclose widening of the curves of the arteries in the longitudinal fissure without lateral displacement. As the dilatation of the ventricles progresses, the arteries show definite widening of the curves. Whether the arterial phase reflects changes or not, the tributaries of the internal cerebral vein, which are located along the lateral wall of the lateral ventricle, show elongation in the lateral and anteroposterior projections. As the degree of hydrocephalus increases, the distance between the

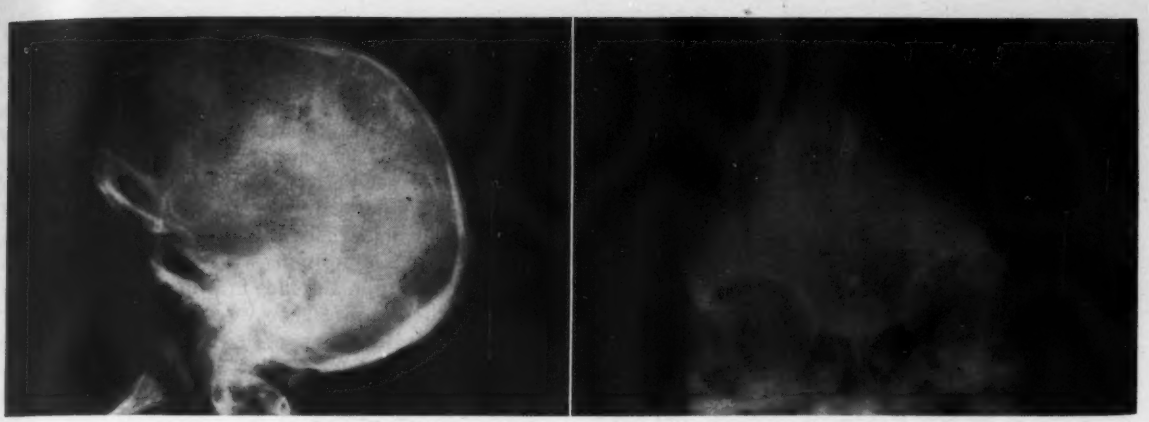

Fig. 5. Visualization of the deep and superficial veins on the second serial film in a case of arteriovenous malformation.

inferior sagittal sinus and the internal cerebral vein increases. The curves of the internal cerebral vein and great vein of Galen are straightened and displaced downward and backward. If symmetrical hydrocephalus is caused by a tumor of the posterior fossa that is obstructing the aqueduct, the basilar vein may be displaced forward and upward. This can be an aid to the diagnosis of cerebellar tumor, which previously was considered impossible to diagnose by carotid angiography.

Johanson[5] contends that deep-seated central tumors involving the basal ganglia, corpus callosum, pineal body, and ventricles can at times be diagnosed solely on the appearance of the deep central veins.

Tumors of the basal ganglia may or may not be accompanied by hydrocephalus. The condition is usually readily distinguished from symmetrical hydrocephalus, since in cases of tumor the internal cerebral vein is displaced across the midline. If arteries of the longitudinal fissure are displaced laterally, the internal cerebral vein is displaced more laterally and usually upward.

The effect exerted on the central veins by tumor of the corpus callosum depends on whether the tumor is located anteriorly or posteriorly. The arteries of the longitudinal fissure are usually, although not necessarily, displaced to the opposite side. When the tumor lies anteriorly, the septal vein and anterior portion of the internal cerebral vein is usually displaced downward and across the midline. The "venous angle of the brain" is more acute, and the striothalamic vein is elongated. When the tumor is located in the posterior portion of the corpus callosum, the posterior portion of the internal cerebral vein is elongated and displaced downward.

If the pineal body is calcified, an increase in distance can be noted between it and the internal cerebral vein in cases of pineal tumor. This distance is normally only a few millimeters. Lateral displacement of the internal cerebral vein is rare, but does occur occasionally. The posterior portion of the vein is elevated and stretched. Any variation or modification in the arterial phase is due to hydrocephalus.

Tumors of the lateral and third ventricles cause changes in the central veins depending on whether the tumor is located above or below the internal cerebral vein. In tumors of the lateral ventricles, which are located above the vein, it is displaced laterally and downwards. When the tumors are located below the vein, it is displaced laterally and upwards. Tumors of the third ventricle cause the internal cerebral vein to be displaced upward. Again, changes in the arterial system are usually due to hydrocephalus.

Tumors of the frontal lobe usually displace the arteries in this vicinity, the type and degree of displacement depending on the exact location and size of the tumor. The anterior cerebral artery and its branches are displaced to the opposite side. It will also be displaced, along with the middle cerebral artery, downward or upward according to the position of the tumor. The central veins are subject to the same mechanisms. The internal cerebral vein is displaced laterally across the midline to a greater degree when the tumor is more posteriorly situated. Comparison of the lateral displacement of the internal cerebral vein and anterior cerebral artery can give an excellent idea of the extent of the tumor. When the tumor is situated low in the frontal region, the anterior end of the internal cerebral vein is displaced upward; when the tumor is high in the frontal area the vein is displaced downwards. It can also be displaced posteriorly if the tumor is located at the frontal pole.

Suprasellar tumors and those occurring in close proximity to the sella turcica displace the arteries of the cerebral system. The carotid siphon is displaced either forward and upward or downward and backwards, depending on the location of the tumor. If the tumor extends far enough laterally, the middle cerebral artery will be displaced upward; and if the tumor extends far enough anteriorly, the anterior cerebral artery will also be displaced upward. Large tumors may affect the deep central veins. If these tumors are located in the midline they will elevate the septal vein and the anterior portion of the internal cerebral vein without lateral displacement. When the tumor is situated lateral to the midline, the appearance of the central veins is similar to that found with tumors in the midline; also the deep central veins are displaced to the opposite side.

Tumors involving the temporal lobe displace the

middle cerebral artery to a greater or lesser degree according to the location of the tumor. Anteriorly situated tumors deflect the artery upward or downward depending on whether the lesions arise above or below the course of the artery. If the tumor lies more posteriorly in the temporal lobe, the degree of arterial displacement is less evident. Laterally placed temporal lobe tumors can displace the middle cerebral artery mesially. The arteries of the longitudinal fissure are usually displaced across the midline. The internal cerebral vein is also displaced across the midline, and usually to a greater degree than the arteries of the longitudinal fissure. The basilar vein of Rosenthal is displaced medially. When the tumor lies in the anterior part of the temporal lobe the anterior end of the vein is deflected upward, and when the tumor is located posteriorly the posterior aspect of the vein is displaced upward.

In parietal and occipital tumors, the arteries of the longitudinal fissure may or may not be displaced across the midline. If the tumor is located posteriorly and in the midline, the posterior portion of the pericallosal artery may be displaced downward. Parietal tumors if situated near the sylvan fissure may depress the sylvan group of vessels from above downward. Occipital tumors may displace this same group of vessels, particularly the angular artery, upward and forward. With tumors in this location the deep central veins should show greater displacement than the arteries. The veins may be displaced laterally, and in midline tumors the deep central veins are depressed from above downwards. The basilar vein of Rosenthal may be displaced medially by parietal tumors or upward and laterally by tumors involving the lateral ventricles.

Angiographic technic

Briefly, the technic[18,20] used in performing cerebral angiography at the Hospitals of the Philadelphia College of Osteopathy is as follows: Preliminary radiographic films of the skull are studied and any pertinent information that can be gained from them is noted. The angiographic examination is carried out by a neurosurgeon and a radiologist, with the assistance of an anesthetist. The patient is placed on the x-ray table in the supine position with the head resting on a Sanchez-Perez rapid serial cassette changer, and sodium pentothal anesthesia is instituted. The neurosurgeon then places an 18-gauge needle in the common carotid artery, either by the percutaneous method or by direct exposure of the artery.

When the needle is properly placed, the radiologist and the x-ray technician position the patient and check all technical factors. The head is placed first in a true lateral position, with the site of injection turned away from the film in order to facilitate the work of the neurosurgeon who makes the injection. The head is them immobilized, and an adjustable cylinder, which has previously been attached to the tube, is lowered into position. This cylinder adds greatly to the quality of films obtained and it also protects the operators from excessive radiation.

When all is ready the neurosurgeon manually injects 10 cc. of 30 per cent Urokon in aqueous solution, in a 2-second interval. On verbal signal from the neurosurgeon, eight rapid serial radiographs are made at ¾ second intervals. The total time from the beginning of the injection to the end of the radiographic procedure is approximately 8¾ seconds. The first exposure is made 2 seconds after commencement of the injection.

The lateral films are developed immediately. The radiologist examines the wet films and decides the next step in the procedure. If the lateral films are satisfactory, the procedure is usually repeated with the head in a modified anteroposterior position. The tube is angulated 15 degrees caudally. After the second injection a film of the abdomen is secured in an attempt to visualize the urinary system.

Variations in procedure are sometimes necessary, depending on the type of case and the clinical status of the patient as observed by the anesthetist and neurosurgeon. For a more detailed account of the procedure, the readers are referred to the work of Ruberg.[20]

Observations made by various investigators vary and conflict. Therefore, an investigator utilizing a particular technic would do well to establish his own individual norms based on his experience and observations in his own series of cases

Clinical studies

The clinical material accumulated for review in this paper included 90 case records selected at random from the files of the Department of Radiology at the Hospitals of the Philadelphia College of Osteopathy. Of these 90 cases 43 were considered nonpathologic and 47 were considered pathologic. The nonpathologic cases were established on the basis of essentially normal angiograms and the absence of intracranial symptoms on clinical laboratory and therapeutic testing. In the pathologic cases, most of the diagnoses were confirmed at operation or by postmortem examination. The exceptions were those few cases that did not warrant surgical treatment.

Of the 47 abnormal angiograms, 8 demonstrated carotid thrombosis and were eliminated from the study because of the impossibility of achieving a satisfactory venous study. In 20 cases the angiograms revealed brain tumors, 15 of which were primary and 5 metastatic. The rest of the cases were distributed as follows: aneurysm, 5 cases; cerebral spasm or arteriosclerosis, 6; arteriovenous malformations, 4;

TABLE I—DISTRIBUTION OF CASES STUDIED BY ANGIOGRAPHY

	10-19	20-29	30-39	40-49	50-59	60-69	70-	Total
Primary tumor			2	1	6	5	1	15
Metastatic tumor				2	1	2		5
Arteriovenous malformations		1	2	1				4
Aneurysm				1	2	2		5
Cerebral spasm and arteriosclerosis			3	2		1		6
Pseudotumor						2		2
Carotid thrombosis			1	2	3	2		8
Hydrocephalus	1							1
Sturge-Weber syndrome		1						1
Nonpathologic	3	9	7	9	10	5		43
								90

pseudotumor, 2; hydrocephalus, 1; and Sturge-Weber syndrome, 1.

Forty-nine of the patients were male and 41 were female. Their ages ranged from 13 to 74 years. Table I shows the distribution of the cases according to age range and clinical status. In 30 of these cases, angiograms were made for the right side only, and in 37 the left side only; in the rest the angiograms were made for both sides.

Analysis of normal cases • In the 43 cerebral angiograms that were considered nonpathologic the circulation time, measured from the time of injection in the common carotid artery to the time opaque medium appeared in the dural sinuses, ranged from 3½ seconds to 7½ seconds, with a mean of 5 seconds. The venous circulation of the brain was satisfactorily visualized without exception in these cases. The superficial veins were usually visualized first; however, in several instances the deep veins were first to be visualized and quite frequently deep and superficial veins were visualized simultaneously on the same exposure. The simultaneous opacification of both deep and superficial veins may have been the result of the length of time between exposures; had the period been less than ¾ seconds this might not have occurred. However, we are at a loss to explain why the superficial veins became opacified first in some cases and the deep veins first in others.

In these normal cases the "venous angle" was rather easily recognized in the lateral position, and usually less readily recognized in the anteroposterior position. The striothalamic vein, the internal cerebral vein, and the great vein of Galen were usually well opacified, as were the veins of Trolard, Labbé, and Rosenthal. The straight sinus was less frequently visualized satisfactorily, and the inferior sagittal sinus was only occasionally visualized. In several instances the vein of the posterior horn, noted by Johanson,[1] was also seen. The peripheral dural sinuses were best visualized in the anteroposterior position.

Analysis of abnormal cases • In the 47 cases considered pathologic, generally the opacification and visualization of the venous phase of cerebral circulation were not nearly as satisfactory or complete as in the nonpathologic group. The circulation time in these cases, when it could be measured, ranged from 2¾ to 8 seconds. In 18 of these cases the venous phase was considered unsatisfactory as an aid in diagnosis because of nonvisualization of the venous system. Included in this group were 8 cases of carotid thrombosis; 3 cases were diagnosed as cerebral spasm, 2 as aneurysm, and 5 as tumor. In the remaining 15 cases of tumor angiograms were considered to be of diagnostic value in 12; and in 3 they were not considered to be of diagnostic aid, because of extremely poor visualization. Therefore in 20 cases of tumor, cerebral angiography was considered as a diagnostic aid in only 12 cases, or 60 per cent. Thus, in our series of cases which is very small, our findings failed to substantiate the importance placed on the venous phase by Johanson[1] and others[6,9,10] in the diagnosis of brain tumor.

In the 12 cases of brain tumor in which the visualization of the venous circulation was satisfactory, changes in the venous system were observed in keeping with the anatomic location of the tumor. Several of these cases showed rather large veins draining the tumor region. In a case of parasagittal meningioma, cerebral angiography was performed before and after surgical treatment. Some time after the operation, regrowth of the tumor was observed at the operative site, and an angiogram showed a markedly vascular tumor growing through the surgical defect in the skull.

It would appear that the most valuable diagnostic information gained in examination of the venous circulation would be in cases of pseudotumor and arteriovenous malformations, and in confirmation of arterial circulation in cases that are not abnormal

In 2 cases of pseudotumor neither displayed any changes in the deep cerebral venous system yet both demonstrated marked displacement of the anterior cerebral artery away from the mid-sagittal plane of the skull.

Of the 5 cases of aneurysm, visualization of the cerebral veins was satisfactory in 3, 2 of which showed good visualization and the third, a case of bilateral carotid aneurysms, only fair visualization.

Six cases were diagnosed as cerebral spasm with or without arteriosclerosis. In 3 of these no venous phase was demonstrated. In the other 3 the venous phase was satisfactory. All 6 cases showed opacification of the internal, external, and common carotid arteries throughout the entire 8-exposure sequence, and the arterial phase was prolonged. The venous phase was demonstrated late and also was prolonged in the 3 cases demonstrating satisfactory opacification.

In the single case of symmetrical hydrocephalus, that of a 13-year-old child, the venous demonstration was excellent. The classic changes previously described in symmetrical hydrocephalus were observed.

In the case of Sturge-Weber syndrome, visualization of the venous phase was poor but demonstrable. Multiple intracranial calcifications conforming to the contour of the gyri were observed. No abnormality of the veins was noted, but transit time of the opaque medium was prolonged.

Four cases of arteriovenous malformation demonstrated satisfactory venous phases. The veins were usually visualized on the first or second exposure following injection, and both deep and superficial veins were usually seen at that time.

Summary

The first portion of this paper was devoted to a review of the literature with reference to the venous phase of cerebral circulation. Embryology, physiology, gross anatomy, and the radiographic findings in nonpathologic and pathologic processes, especially tumor, were discussed. The second portion of the paper deals with the radiographic findings in 90 cases of cerebral angiography selected from case records in the files of the Department of Radiology at the Hospitals of the Philadelphia College of Osteopathy. These cases were reviewed and discussed in relation to the venous phase of cerebral angiography.

Conclusions

1. The physiology of cerebral circulation is not fully understood. It is influenced by local, systemic, and technical factors. More investigation along these lines would seem necessary.

2. The anatomy of the deep and superficial cerebral veins is relatively constant, but anatomic variations are numerous.

3. It would appear that the most valuable diagnostic information gained in examination of the venous circulation of the brain would be in cases of pseudotumor and arteriovenous malformations, and also in confirmation of the arterial phase of circulation in cases that are not abnormal.

4. Because of the poor percentage of satisfactory visualization of the venous cerebral circulation in our series of brain tumor cases subjected to cerebral angiography, it is believed that the diagnosis of brain tumor must generally be based on the arterial phase of this examination. Additional information can be gained as to extent and location of the tumor when the venous phase is satisfactorily demonstrated.

Brentwood Hospital, 4110 Warrensville Center Road

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Use of styramate in common joint and muscular afflictions

ROBERT W. JOHNSON, D.O., Appleton, Wisconsin

Low-back pain and other common joint and muscular afflictions, repeatedly seen in everyday office practice, are frequently associated with skeletal muscle spasm. For treating these conditions, many muscle relaxant drugs are available. Unfortunately, some of these drugs are inconsistent in effect, while others are too fleeting in action. My own experience with several of these agents substantiates the published warnings and cautionary statements. Mephenesin, for example, requires large doses for optimum effect (two to six tablets, 0.5 gram, repeated three to five times daily). Taken in these quantities, it will cause dizziness and lightheadedness unless administered after meals or after the patient has drunk milk or fruit juice. Another drug, methocarbamol, may cause dizziness, lightheadedness, and nausea when employed in the recommended therapeutic dosage of eight to nineteen tablets daily (0.5 gram). Still others may cause excitation or depression, toxic effects on the blood, liver, and renal system, skin rash, and definite hypnotic effects.

Styramate, however, is a true muscle relaxant, acting directly on the extrapyramidal pathways, and is therefore free from hypnotic effects. Results are achieved on the low dosage of one or two 200 mg. tablets, three or four times daily. There are no known contraindications and, in my experience, the drug has not produced depression, excitation, drowsiness, or dizziness. Styramate has longer action and appears to be consistently effective in treating conditions where true skeletal muscle spasm exists. Pharmacologic studies[1] have shown it to be well tolerated, with no untoward effects being noted in liver, bone marrow, or kidney function tests. More recent studies[2] indicate that styramate, in addition to its spinal action, also exerts an effect upon the supraspinal levels involved in hyperkinetic states.

Clinical trial

This study reports on 80 patients, all with typical low-back, joint, and muscular symptoms. There were 50 males and 30 females, ranging in age from 20 to 57 years. All patients were given 200 mg. tablets of styramate,* one or two tablets two to four times daily. In some cases, patients were started on two tablets four times daily and the dose reduced as clinical improvement was noted. Osteopathic manipulative treatment and shortwave diathermy was used in all cases as concomitant therapy.

The clinical results are shown in Table I.

TABLE I—CLINICAL RESULTS WITH STYRAMATE

Diagnosis	Number of patients	Results: Good to excellent	Results: Fair to satisfactory	Results: Fair to poor
Acute lumbar strain	51	40	10	1
Traumatic lumbar strain	3	3	- -	- -
Chronic lumbar strain	1	- -	1	- -
Acute torticollis	9	8	- -	1
Acute lumbar myositis	3	3	- -	- -
Acute lumbar strain with sciatic radiation	3	2	1	- -
Acute cervical dorsal strain with brachial neuritis	1	1	- -	- -
Dorsal cervical strain, right	1	- -	1	- -
Acute low back syndrome with sciatic neuritis	1	- -	1	- -
Acute lumbosacral strain with sciatic neuritis	3	2	- -	1†
Upper dorsal cervical myositis	1	1	- -	- -
Acute middorsal strain	2	2	- -	- -
Acute sacroiliac strain with sciatic neuritis	1	1	- -	- -
Totals	80	63 (79%)	14 (17%)	3 (4%)

*Styramate used in this study was supplied as Sinaxar by Armour Pharmaceutical Company, Kankakee, Illinois.
†Showed marked degenerative changes in the lumbar bodies.

Unlike the other relaxants previously prescribed, styramate was found to be completely free of side effects in the entire series.

Case reports

Case 1. A 43-year old man was first seen in February 1956 for acute pain in the lumbosacral area. He had experienced a sharp pain while turning the filter rolls on a paper machine. Along with acute pain there was evidence of acute lumbar spasm. His past history included an episode of infantile paralysis at the age of 18 months. Residual symptoms from polio were exhibited by a limp in the left leg. Tendon transplants had been made at an early age, which accounted for sufficient improvement to permit him a normal amount of physical activity. On physical examination, the patient found it difficult to walk, sit, or rise from a sitting position. Considerable myositis was apparent, causing him to lean to the left. There was muscular spasm throughout the lumbar area, predominantly over the lumbosacral region. He was restricted in his movements and had pain on flexion and sidebending to the left. Other physical findings were essentially negative. On x-ray examination, there appeared to be no scoliosis or rotation of the lumbar vertebrae. There were rather marked changes of degenerative arthritis in the lower thoracic and lumbar regions, and particularly marked spurring on the third lumbar vertebra. There was nothing to suggest old or recent fracture. The sacroiliac joints appeared to be relatively normal. The diagnosis was acute lumbar strain.

In November 1957 this patient appeared again with a similar complaint. This attack was somewhat milder. Both these episodes were treated with osteopathic manipulation, short-wave diathermy, and analgesics. On July 6, 1959, the patient was seen again for acute pain following an injury to the lumbosacral spine caused by reaching and twisting while in a kneeling position. This was by far the most acute attack he had suffered. For two days he received mephenesin, 1.0 gram three times a day, as well as osteopathic manipulative treatment and short-wave diathermy. On the third day, after showing no marked improvement, he was put on styramate, while continuing to receive osteopathic manipulative treatment and short-wave diathermy. Within 48 hours there was marked improvement. After five days of this combination therapy, the patient was well enough to return to work. Treatment was continued for a total of seven days.

Case 2. A 28-year old woman was first seen in December 1953. At that time she was in acute distress from pain in the lumbosacral region following bending and lifting during house cleaning. Physical and x-ray findings at that time included the following: The patient found locomotion difficult and experienced acute pain on attempting to stand, lie down, or rise from a chair. There was acute tenderness over the lumbar area with evidence of considerable muscle spasm. Flexion of the spine was not too painful, but lateral sidebending produced considerable pain, both right and left. Raising of either leg produced pain in the lumbar area. There was no roentgenographic evidence of scoliosis or rotation. The lumbar and thoracolumbar curves were very flat and the lumbosacral angle rather obtuse. There was a small spur on the anterosuperior margin of the fifth lumbar body. Behind the disk space between the fourth and fifth lumbar vertebrae, seen only in the lateral view, there was a curved shadow, linear, fairly thick, running from the posteroinferior margin of the body down behind the shadow of the upper margin of the fifth lumbar body, and at a slight distance from the posterior margin of the fifth lumbar body. No other unusual findings were noted. The upper portion of the sacrum was essentially normal. The cause of the peculiar calcification between the fourth and fifth lumbar vertebrae was uncertain. One would think of a calcification in the annulus or in an extruded disk or some unusual type of calcification in the dural sac. It seemed that calcification associated with disk protrusion was the most likely.

The diagnosis at that time was acute lumbosacral strain with possible disk protrusion. Treatment of this first episode consisted of osteopathic manipulation and short-wave diathermy. The patient responded satisfactorily within 7 days, but was seen periodically for the next 2 or 3 weeks.

The patient was again seen in November 1958, exhibiting acute symptoms of lumbar myositis. She was unable to get out of bed. Treatment consisted of styramate, two tablets three times daily, analgesics, and osteopathic manipulation. Within 24 hours the patient was free of muscular spasm and much more comfortable. She was able to get out of bed on the third day. Osteopathic manipulative treatment and styramate were continued for a total of 7 days.

Discussion

All cases included in this study were of the acute type frequently seen in routine osteopathic practice. The patients complained of typical symptoms of low-back pain such as backache occurring over the lumbar vertebrae, lumbosacral area, sacrum, sacroiliac region, and coccyx. Some associated conditions were marked degenerative changes in lumbar bodies, congenital abnormality of fifth lumbar vertebrae, moderate arthritis, and thinning of the lumbosacral disk spaces (as revealed by x-ray). Eleven of these patients had suffered frequent attacks in the past. Styramate was prescribed for all these patients after examination and diagnosis. In addition, osteopathic manipulative treatment was given, followed by short-wave diathermy in most cases. Because of its muscle-relaxant properties, I have found styramate to be an asset to osteopathic manipulative treatment. Following treatment, patients on this medication were found to be more comfortable. The length of disability was decreased and rate of recovery was accelerated.

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Special problems of the newborn*

NELSON D. KING, D.O., F.A.C.O.P., Associate Professor of Pediatrics, Kirksville College of Osteopathy and Surgery, Kirksville, Missouri

Over 300 years ago Sir Thomas Browne wrote, "Every man is some months older than he bethinks him; for we live, move, have a being, and are subject to the actions of the elements, and the malice of diseases, in that other World, the truest Microcosm, the Womb of our Mother."[1] As pediatricians we have a special obligation to understand as completely as possible the human organism in its fetal and newborn stages. We can then begin to understand what must be done to help the infant survive in its extrauterine state. I wish to discuss today some special problems of the newborn that we sometimes are prone to forget. The problems will be grouped according to three perinatal etiologic influences: genetic, environmental, and physiologic. The term "perinatal" means the whole birth process, from conception through parturition—in other words, the prenatal, paranatal, and neonatal periods in the life of an infant.[2]

The great increase in our medical knowledge, as given to us by clinical and basic science investigators, has created difficulties for the pediatrician and the obstetrician. So rapid are the developments that we find it almost impossible to keep up with them. Yet we must be as completely informed as we possibly can as to the possibilities for preventing complications that may arise in the whole perinatal period. We need team action—a team composed of the obstetrician, the pediatrician, and the general practitioner,[2] who will coordinate their special skills in a unified effort to prevent injury to the infant both before and after birth. Abnormal conditions may occur in any pregnancy, but will not be detected unless specifically searched for. What we do not look for, we do not find.

*James M. Watson Memorial Lecture, presented at the annual meeting of the American College of Osteopathic Pediatricians, Detroit, February 10, 1959.

It should be borne in mind, of course, that many of the problems of the newborn cannot be separated according to distinct etiologic factors. Genetic flaws can lead to abnormal physiologic development, which in turn is further influenced by harmful agents in the environment. Genetic and environmental conditions profoundly influence fetal and neonatal development; hence, many congenital defects cannot be traced to any single cause. Nevertheless, real progress is being made in preventing or modifying these afflictions, as the result of basic and clinical studies related to the total care of mother and infant.

Genetic problems

What effect does genetics have on the growing unborn infant which will present a special problem for the newborn? The geneticist often refers to the inheritance of a trait, meaning the inheritance of a primary gene which in some manner controls the development of a characteristic. This control can be affected by other genes or by an environmental factor. The infant's inheritance, therefore, comprises a genetic complex which in its effects may be specifically modified by certain environmental conditions. The rate or degree of cell differentiation or growth is governed by genetic action; as a consequence of this influence, an organ or a limb may be incomplete, or doubled, or perhaps entirely absent. There is some evidence that such disturbance in growth reflects a hormonal influence which is under genetic control.[3] The genetic control of metabolism in man has been fairly well established. For example: Normally phenylalanine is oxidized to tyrosine. If the amino group is replaced by oxygen it is transformed to phenylpyruvic acid. Some persons (phenylketonurics) are unable to complete the oxidation to tyrosine; phenylpyruvic acid accumulates and is excreted in the urine, along with phenylalanine and phenyllactic acid. This metabolic fault is inherited recessively and causes many cases of so-called feeblemindedness.[3] The same type of process occurs in the

The inheritance of a trait means the inheritance of a primary gene which in some manner controls the development of a characteristic. This control can be affected by other genes or by an environmental factor

alcaptonurics, where again an enzyme seems to be lacking. Tyrosine is oxidized and finally converted into melanin. An albino is unable to make this conversion. Albinism is a recessive characteristic reflected in the congenital absence of pigmentation of the skin. Because the enzyme typrosinase is missing, tyrosine cannot be converted to melanin.

Adrenal insufficiency is an inherited metabolic defect that leads to a syndrome involving hyperkalemia, hypochloremia, hypovolemia, and hypotension. In former times this condition invariably resulted in death of the infant, but successful treatment is now possible if the diagnosis is early and the treatment thorough.[4] In most cases the affected infant shows an adrenal crisis at the age of 6 or 7 days, and treatment should be instituted at once, by means of salt infusions, desoxycorticosterone acetate (DOCA), and cortisone. With adequate treatment, the infant's condition is usually stabilized at 3 to 4 months of age; consideration should then be given to the slow elimination of DOCA and cortisone, or continuing maintenance treatment with long-acting DOCA. It may be necessary to continue treatment for years or perhaps for life.

Cystic fibrosis of the pancreas is a genetic disease which can be modified in its course by appropriate treatment. Early diagnosis is essential, and depends on an adequate family history from the pediatric standpoint.[2]

When an infant is born with a genetic defect, particularly one involving the malformation or absence of a limb or an organ, the parents will naturally want to know what the chances are that their next child will be so affected, and how severe the affliction is likely to be. Many prospective parents realize that they do carry a trait that may be hereditary. If two such parents have heterozygous genetic tendencies, the chances are one in four that their children will be affected by the hereditary trait. The severity of the defect of a genetically transmissible trait varies; however, a probability can be estimated on the basis of the family history. If an infant lacks feet, for example, or the fingers of a hand, and the severity of the trait can be studied in other members of the family, an estimate can be made in order to help the parents.[5] Recognition of a hereditary defect in a newborn child requires that all the child's siblings be examined early and frequently, so that the pediatrician will have some indication of the chances for others.

Environmental problems

Environment can affect the fetus in such a manner as to cause characteristics which at present can hardly be diffentiated from known hereditary states. Deaf mutism is known to be inherited in some families, but it may also be caused by scarlet fever or other diseases which occur early in childhood, before the child has learned to speak. The effect of rubella in the mother during the early weeks of the prenatal period is well known; equally well known are the effects of syphilis, which is now controlled by premarital serologic testing. It is now believed that to the list of viral and bacterial influences can be added many toxic elements such as are found in common household medications. These can cause many of the common defects in the early stages of embryonic development, such as microphthalmus, corneal opacities, cataracts, heart defects, harelip, cleft palate, and so on.

Hydrocephalus, microcephalus, chorioretinitis, and other defects have been found to be associated with protozoan infections such as toxoplasmosis. Infantile cirrhosis also must be considered an environmentally induced disease, since the virus that causes neonatal hepatitis leading to cirrhosis is prenatally transmitted, through the placenta. Since the virus, in the first place, is probably introduced into the maternal blood stream by contaminated transfusion equipment, it is imperative that the physician observe strict precautions in order to prevent infantile cirrhosis. The Coxsackie group B virus has been found to be implicated in severe cases of myocarditis and myocardial insufficiency. This is a postnatal complication most likely to occur through exposure of the newborn infant to persons suffering from infection by a Coxsackie type of virus.

What about radiation of the fetus in utero and its effect on the newborn infant? This is a controversial question, but it is generally agreed that radiation exposure should be prevented at least until the fifth or sixth month of gestation. Microcephaly has been associated with early exposure to radiation; other disturbances in brain development have likewise been traced to the direct effects of radiation in the fetus.[2] X-rays, if they must be used early in pregnancy, should be accompanied by adequate shielding of the fetus, and routine pelvimetry should be deferred until the seventh month of gestation. It is entirely possible that radiation effects have caused severe developmental defects when used at the beginning of pregnancy, before the condition is known to the patient or her physician. During the first 3 or 4 weeks of embryonic development, any and all of the toxic influences that have been mentioned here may produce severe developmental defects.

Among the biochemical conditions that are deleterious to prenatal development, anoxia is probably the most common.[2] The resulting injury to involved tissues leads to varying manifestations, according to the stage of fetal development at the time of injury.

The ingestion of excessive amounts of vitamin B_6 may lead to alterations in the fetus or the newborn infant. Studies in animals have shown that certain vitamin deficiencies also may result in congenital anomaly, but there is as yet little evidence on this point in relation to human beings. Convulsive disorders may result from pyridoxine deficiency in the newborn. In the prenatal period, excessive intake of vitamin D by the mother may lead to severe hypercalcemia in the infant, and to permanent brain damage.

When there is a history of cretinism in the family, or of maternal thyroid disease, thyroid dysfunction may appear in the newborn infant. To prevent the arrest of brain development in the infant the circulating hormone level in the mother should be measured by means of the protein-bound iodine (PBI) test, and replacement therapy instituted to maintain the blood level of PBI at 8.3 gammas per 100 cc., the mean level characteristic of pregnancy. In such cases the newborn infant should be examined for cretinism, which may be signified by a PBI level of 2 to 3 gammas. Prompt treatment is essential to the normal growth and mental development of the child.

Although prevention is not always feasible, as in such conditions as clubbed foot, obstructive uropathy, and adrenal hyperplasia, much can be done to alleviate these disorders. The early diagnosis of the adrenogenital syndrome in the female infant, for example, and prompt treatment with steroid hormones, will prevent subsequent psychologic trauma and dwarfing.[2,5] As Cooke[2] points out, the routine care of well children may so blunt the pediatrician's fine perception that some of these congenital disorders may escape recognition. It is necessary that he maintain a high index of suspicion.

Diabetes in the mother greatly lessens the chances for the healthy development of her offspring, even when the diabetes is well controlled.[2,6] If when the mother approaches term the diabetes is poorly controlled, and particularly when ketosis is present, the chance that the infant will survive is less than 1 in 25. In such cases the fact that the infant is relatively large does not necessarily indicate normal full development, and the newborn infant must be cared for as if the birth were premature.

The newborn infant has many special problems related to obstetric factors. Toxemia of pregnancy may lead to neuropsychiatric disorders in the child later on. Breech presentation, with attendant difficulties in delivery, may be responsible for injury such as brachial plexus paralysis.[2] When there is considerable cephalopelvic disproportion there may be injuries leading to brain damage in the infant.[7] Hazards also arise from premature separation of the placenta, placenta previa, prolapse of the cord, and precipitate labor.

Grave obstetric problems may arise from severe anoxia in the infant, as well as mechanical trauma. The routine use of oxygen for the patient in labor should be mandatory, and it is extremely important also that the fetal heart rate during labor be carefully checked, to detect early fetal distress that might lead to serious brain damage. Anoxia is more likely to occur just before or during delivery than in the postnatal period; the aspiration of amniotic content just before delivery is a significant cause of respiratory distress possibly leading to brain hemorrhage and medullary failure occurring from 6 to 12 hours after delivery.

It is becoming apparent that the newborn infant is physiologically "immature" only in comparison with the older child or adult; for his own immediate needs his physiologic functions must be considered adequate

Physiologic problems

The physiologic development of the infant in its prenatal period is of paramount importance in relation to special problems of the newborn.[1] With increased knowledge of prenatal physiology, our interests deepen and we have a better opportunity for understanding those problems. Basic knowledge of the development of fetal structures and immunologic mechanisms is especially necessary for the physician's comprehension of the difficulties confronting the prematurely born infant. Then too, the great alterations and adjustments that must take place in the fetal structures immediately following birth have special significance for the pediatrician.

It is common practice to refer to the newborn as being physiologically immature. This term has been based on what is normal for the adult, however, rather than the infant. As literature accumulates on the physiology of the newborn, it becomes apparent that the newborn infant is physiologically "immature" only in comparison with the older child or adult; for his own immediate needs his physiologic functions must be considered adequate. On this basis it can be more easily recognized that actual functional immaturities do appear in the newborn infant, and that exaggerations of such states constitute pathologic disorders that may prove fatal. Many of these metabolic disturbances are difficult to evaluate, however; tests are still lacking for the localization and characterization of function, in many instances. We have all had the experience of failing to detect specific pathologic states in postmorten examinations of infants who have died soon after birth. It is sometimes baffling for the physician to try to explain a death on the basis of the gross or even the microscopic findings. Current research offers increasing evidence, however, on the biochemical and physiologic bases for these perplexing problems. As more funds become available, research can be centered less on clinical aspects and more on aspects of basic

science, where many sought-for solutions still lie hidden.

The tendency for the premature infant to incur hyaline membrane disease has recently been found to be associated with extremely low levels of free and total profibrinolysin.[8] The deposit of fibrin in the lungs probably results from various conditions, but the infant's inability to recover from the illness is thought to be due to the low level of profibrinolysin in the plasma. What is needed, then, is some way to increase the plasma level of profibrinolysin, or to discover some sort of fibrinolytic enzyme that might be administered either parenterally or directly into the respiratory tract. Such a fibrinolysin is "plasmin," recently reported[9] as having been used with encouraging results. The substance was instilled into the respiratory tract, and the hyaline membrane became dissolved. This study also brought out the fact that the maternal fibrinolytic enzyme system is distinctly separate from that of the infant. Although the infant's own fibrinolytic system seems to be adequate under normal conditions, a deficiency in this respect may be responsible for impairment of hemostatic function in some newborn infants. Concentration of plasma fibrinogen is at a low level in infants as compared with adults. Here again there is apparently no relation between the plasma levels in the mother and the prenatal infant.

With regard to hyaline membrane disease, therapeutic procedures have not changed in recent years except for the introduction of plasmin. Immediate causes of death in newborn infants probably are multiple, and may include respiratory acidosis, deficient oxygenation, and possibly physical exhaustion from extreme dyspnea. Acute cor pulmonale has been observed, resulting from the atelectasis of hyaline membrane disease. It is important, in patients with this disease, that cardiac rate and function be observed, as well as respiratory rate; digitalis may be helpful. Osteopathic manipulation can assist gaseous exchange and phagocytic action. The need for autopsy studies to determine contributory factors in so-called atelectasis deaths can hardly be overemphasized.

The problem of cerebral damage from anoxia in the newborn may well have a physiologic basis underlying even the possible traumatic and chemical factors. The more one sees of the newborn infant and his efforts at survival, the more impressive is the fact that such an infant has a tremendous capacity to survive prolonged anoxia without any residual. This ability may result from the fact that growth and metabolism in the fetus are carried on in a very low oxygen tension. But on the other hand, there are occasional cases of severe cerebral damage without any history of anoxia in the perinatal period, suggesting that the mechanical or chemical effects of anoxia may be merely the reflection of a fundamental defect. Here is an area that should be investigated, perhaps with reference to the enzyme systems in their association with brain metabolism. It is possible that the glycolytic and various oxidative enzymes[3] have a protective effect, or promote a mechanism that allows the human fetus to undergo relatively long periods of anoxia without damage.

The whole process of maturation of special functions is of great clinical interest. Although the significance of enzymatic adaptation is suspected to be great, little is actually known about its influence during the perinatal period in either normal or pathologic states

Studies of enzyme systems and their effects on the nervous system[3] have revealed clinically significant patterns in the maturation of central nervous system metabolism. As indicated above, the fetal enzyme system appears to protect the brain against anoxia for a while after birth; heat-regulating and circulatory mechanisms are probably involved in the process. In the very young infant, the limited respiratory response to increases in carbon-dioxide tension in the blood may be due to immaturity of the medullary centers. All of these physiologic phenomena are related in some way to the integrity of the blood-brain barrier, which also is incompletely developed at birth. In the neonatal period this barrier is relatively permeable to bilirubin and protein, and probably to other substances such as antibiotic agents and intermediary metabolites. The increased permeability of cerebral vessels may be due to perinatal damage or to immaturity; the dynamics and development of the blood-brain barrier are not completely understood as yet. Current research indicates, however, that here too any neonatal peculiarities may reflect the incomplete development of enzyme systems.

Functional immaturity of the enzyme systems within the liver parenchyma may be responsible for the physiologic jaundice which occurs in about two thirds of all full-term infants during the first few weeks of life. The condition is characterized by a slight elevation of serum bilirubin by the fourth day, the elevation being more marked in premature infants and in those with hemolytic disease. It is generally agreed that hyperbilirubinemia[10] is not caused by a simple decrease in the erythrocyte count or packed-cell volume, but may be related in some way to hepatic immaturity based on the malfunction of enzyme systems. Abnormalities of hepatic function, signified by physiologic jaundice, may lead to the cerebral disturbances that result in kernicterus or hepatic coma, two major clinical entities that are not at present fully understood. Kernicterus is marked by degeneration and pigmentation of the neurons, with an elevated level of indirect reacting bilirubin in the plasma.

The combination of impaired hepatic function and incomplete blood-brain barrier is thought to permit toxic substances to accumulate in the blood and thus

gain access to the brain. Elevated concentrations of ammonia in the blood during the neonatal period, associated with bacterial activity in the intestine, are thought to cause some of the cerebral symptoms in severe hepatic disease. In this instance the ammoniacal products may be absorbed and not become detoxified because of impaired liver function. Such considerations must be added to our past knowledge in reference to etiologic concepts of brain damage with its resultant cerebral palsy.

Much remains to be learned about the validity of the traumatic theory of intracranial damage.[7] A recent report on learning disabilities in children[11] cites many interesting cases observed in nursery schools by teachers and psychologists. These children had little motor involvement but did show difficulty in speech, hearing, writing, and reading, and with improper handling all of the children involved could become severely maladjusted. The case histories consistently showed prematurity, early mild spastic hemiplegia, definitely traumatic delivery, skull fracture at birth, difficult breech extraction, and Rh incompatibility resulting in mild erythroblastosis. These are the traumatic factors that have long been considered the main causes of brain damage in children. Arbuckle[12] has stated that the most common predisposing factor in physical and mental disturbance is structural malalignment resulting from birth trauma. Further work is needed, however, to determine whether such trauma is entirely physical or whether it reflects a physiologic influence exerting toxic chemical or metabolic effects. The addition of cranial technic to osteopathic manipulative therapy has undoubtedly assisted in reducing the tension at the cranial-vertebral junction, but we need to know a great deal more about whether this effect has been produced by physical or chemical means.

The gastrointestinal tract also gives rise to certain special problems in the newborn infant. What can the infant digest and absorb? Formerly it was believed that the infant's gastric enzyme system and absorption mechanisms were deficient, but it is now generally believed that the gastrointestinal secretions and enzyme activities in the newborn do permit broad rational feeding for the normal infant.[3] The results of specific studies vary greatly, however; the only point of agreement at present seems to be that maturation of function of amylase and lipase is delayed somewhat in the neonatal period.

The whole process of maturation of special functions is of great clinical interest at present. Although the significance of enzymatic adaptation is suspected to be great indeed, little is actually known about its influence during the perinatal period in either normal or pathologic states.

Prematurity is always a serious problem. With regard to body heat mechanisms, it is still not known[13] whether premature infants are temporarily poikilothermal in the early neonatal period or whether they are homothermal, exhibiting a slight increase in metabolism in response to a fall in temperature. In utero, the infant is in a liquid medium at approximately 98.6 F. After delivery the infant's environment ranges from 74 to 80 F, representing a drop in temperature of some 20 degrees. Here is a special problem of the newborn. A premature infant should be placed immediately in an environment providing a temperature of about 89 degrees. It has been shown[13] that infants are more likely to survive at this temperature than in the so-called hypothermal range of 84 F. Humidity is equally important, and should be maintained at approximately 90 per cent.

Another special problem of the newborn, and especially the premature infant, is susceptibility to infection. Studies of the incidence of bacterial infection[14] in newborn infants indicate that major infections occur in this group with relatively very high frequency. Most serious are those caused by resistant staphylococci, which continue to be difficult to combat. In some clinics, however, moniliasis is still the most common infection of the newborn. Adequate control of the infection in the infants, however, can usually be obtained by appropriate treatment of vaginal moniliasis in the mother, during the prenatal period. This can be accomplished by the newer fungicidal medications, particuarly nystatin. With such prophylactic measures moniliasis of the newborn should occur only rarely.

Postmaturity, in which the gestational period is prolonged to 43 weeks or more,[15] also holds special problems for infant and mother. Clifford[16] comments as follows:

> Postmaturity per se is a very common condition. Of all pregnancies, 25 per cent extend to 41 completed weeks of gestation, 12 per cent to 42 weeks, and 5 per cent to 43 completed weeks or over. . . . If one plots the incidence of pregnancies terminating at various gestational ages, on the one side is prematurity with an incidence of 6 per cent and on the other postmaturity with an incidence of 5 per cent; the resulting parabola resembles the curve of normal distribution.

The reason for postmaturity may be the failure of the progesterone level to fall, or some constitutional and hereditary factor, or an endocrine disorder in the mother. Probably the immediate predisposing factor, however, is failure of the normal mechanism enabling the infant's head to descend into the mother's pelvis. Cause of the failure could be cephalopelvic disproportion, the presence of tumors, transposition or malposition of the fetus, occiput posterior, and so on. The condition is serious only when the placenta is inadequate, with resulting malnutrition and anoxia in the infant. Although the detection of placenta dysfunction is problematic, it is known that the condition occurs most often in the elder primipara and is marked by diminution of the amniotic fluid and shrinking of the uterus. If there is fetal anoxia the amniotic fluid will be meconium stained.

The term dysmaturity is now preferred by some[17] as more specific than "prolonged pregnancy" or "postmaturity." When the condition is serious there is a decrease in oxygen saturation in the cord blood, and an increase in hemoglobin, plasma pentoses, protein-bound hexoses, bilirubin, and nonprotein nitrogen. Clifford[16] states further that there is no sure way to determine placental dysfunction before the birth of the postmature infant, although suggestive findings might be a reduction in circumference of the maternal abdomen and reduction in distance be-

tween the symphysis and the height of the fundus. If by means of abdominal tap it is discovered that the amniotic fluid is meconium stained, immediate cesarean section is recommended. In view of the reduction in quantity of amniotic fluid, however, it may be very difficult to puncture the amniotic sac in order to obtain a specimen. Fetal electrocardiographic studies, which would reveal myocardial ischemia, may help in diagnosing placental dysmaturity.[17]

Neonatal anemia resulting from fetal hemorrhage into the maternal circulation is a very serious problem of the newborn.[18] If transplacental hemorrhage has occurred, the infant will be pale, hypotonic, and lethargic. Fetal hemoglobin in the mother's peripheral blood will be elevated to 2 per cent or above, and nucleated fetal erythrocytes may be noted in the maternal placental spaces, in microscopic sections of the placenta. An important diagnostic sign is jaundice in the mother just before delivery, with a systemic reaction suggestive of the transfusion of incompatible blood. The treatment of this type of anemia in the infant is simple transfusion of whole blood.[19] With regard to the use of a coagulant agent in infants, vitamin K and vitamin K_1 of the fat-soluble type appear to constitute the ideal preparation for routine use. These vitamins produce a prompt shortening of the prothrombin time and are superior to water-soluble synthetic vitamin K in this respect. The recommended dose is 1 mg., intramuscularly; doses above this may cause hyperbilirubinemia in some patients.

Summary

Although the problems of medical care of newborn infants are highly complex, they may conveniently be discussed according to three perinatal influences: genetic, environmental, and physiologic.

The genetic control of cell differentiation and growth has long been recognized as underlying such congenital defects as malformation or incomplete development of organs and limbs, but little is known as yet about the possibility of preventing the occurrence of these inherited traits. The genetic control of metabolism has more recently come under study, and certain diseases formerly thought incurable are now yielding to treatment aimed at replacing missing factors. Phenylketonuria (now recognized as the cause of some types of feeblemindedness), congenital adrenal insufficiency, and cystic fibrosis of the pancreas are among the diseases amenable to appropriate treatment. Regarding genetic problems in general, the physician should be able to inform parents about the probabilities that hereditary traits will be transmitted to future offspring.

Environmental influences threatening the health or life of the newborn infant cover a wide range: effects of diseases in the mother during pregnancy, direct or indirect effects of viral and bacterial activity, toxicity caused by various chemicals, radiation damage to the fetus in utero, metabolic defects or imbalances in the mother, and nutritional phenomena. Diabetes or thyroid disease in the mother are especially important with regard to the newborn infant. Obstetric problems such as toxemia of pregnancy and various mechanical difficulties associated with delivery account for many medical problems in the newborn. Current research is shedding light on possible fundamental elements in some of these conditions.

Basic knowledge of prenatal and neonatal physiology is of paramount importance to the pediatrician. Understanding physiopathology depends on thorough understanding of fetal structures and immunologic mechanisms in the normal state. Much in this field is very new and receiving greatly increased attention in research centers at present. Hyaline membrane disease, for example, has been found to be associated with low levels of profibrinolysin; administration of fibrinolytic enzymes has brought gratifying results. It now appears that enzyme systems and mechanisms are intimately bound up with most of the neonatal disturbances, such as central nervous manifestations, that were formerly thought to be structural or traumatic in origin. It is now recognized too that the special problems of postmaturity, as well as those of the premature infant, require the physician's careful attention.

Care of the infant during the whole perinatal period requires the special skills and knowledge of a team consisting of the obstetrician, the general practitioner, and the pediatrician. Abnormal conditions must be constantly guarded against, to prevent insofar as possible the injuries that give rise to special problems for the newborn.

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Cesarean section
A continuation study*

THEODORE H. FREILICH, D.O., Philadelphia, Pennsylvania

The purpose of this study is to review the cesarean sections performed at the Metropolitan Hospital in the years 1953 through 1958, analyze them, and compare the findings with those of the preceding 6 years, 1947 through 1952, reported previously.[1]

During the period under consideration, 5,305 patients were delivered, in the course of which 277 cesarean sections were performed. This is an incidence of 5.2 percent. The incidence of section in the previous study was 3.8 percent; the combined figures of 8,145 deliveries and 385 sections in 12 years have an over-all rate of 4.7 percent. Waters[2] feels that an incidence of 5 percent is proper. A study of the years 1950 through 1955 showed that several institutions, reporting a similar amount of work, had section rates of 5 to 6 percent.[3]

Table I gives the rate of cesarean section for each year included in this study.

TABLE I—RATES OF CESAREAN SECTION

Year	Live births	Cesarean sections	Percentage
1953	706	33	4.6
1954	726	28	3.9
1955	763	42	5.5
1956	918	38	4.1
1957	1057	68	6.4
1958	1135	68	5.9
Totals	5305	277	5.2%

Indications

The most frequent primary indication for section in this series was previous cesarean section (101 cases). The next most frequent indication was cephalopelvic disproportion (64 cases). This condition was diagnosed by routine x-ray pelvimetry, and test of labor was given when indicated. Clinical judgment was usually confirmed roentgenographically, as in the multiparous patient in active labor who failed to make adequate progress.

Breech presentation in a primipara was next in frequency, 39 cases of this type being managed by section.

Other primary indications for section are seen in Table II.

TABLE II—PRIMARY INDICATIONS FOR CESAREAN SECTION

	No. cases
Previous section	101
Cephalopelvic disproportion	64
Primiparous breech	39
Abruptio placentae	17
Placenta previa	15
Abnormal presentation	10
Toxemia	10
Cervical dystocia	10
Elderly primigravida	9
Fetal embarrassment	7
Uterine inertia	5
Breech, no progress	2
Atrophic hip	1
Osteomyelitis of hip	1
Psychiatric	1
Nephritis	1
Previous colporrhaphy	1
Breech with previous prolonged labor	1
Ruptured uterus	1
Ectopic kidney	1
Valuable baby	1
Fibroid obstructing labor	1

It is to be noted that fetal distress, which was not found in the previous study, is here listed for 7 cases. This seems to indicate a new awareness of the fetus as an individual, coupled with more attentiveness to fetal heart tones and their variations.

Secondary indications were considered to be con-

*From the Department of Obstetrics, Metropolitan Hospital, Philadelphia.

ditions complicating or in addition to the primary indication for cesarean section. These included diabetes, in 2 cases, and prolapsed cord, in 1 case.

Discussion

The general policy of the Department of Obstetrics is the conservative: "Once a section always a section." Repeat sections are performed 10 to 14 days prior to the estimated date of confinement if the fetus is judged to be of proper size.

In view of the rapidly increasing incidence of repeat section, from 16 percent in 1947 to 1952 to 37 percent in 1953 to 1958, it becomes a matter of obstetric judgment to determine when a patient is at term. The calculation based on the date of last menstrual period is notoriously unreliable, and radiology at present cannot give an accurate answer, although the presence of the femoral epiphyses may be of some help. The obstetrician must be able to evaluate, on the basis of palpation, the size of the fetus.

If the patient is obese and palpation is not feasible, better judgment would be to permit the patient to go into labor before performing the section.[4] The risk of a ruptured uterus is slight if labor is not permitted to continue, since most uteri which rupture do so about a month prior to term, or during active labor. There is, however, the very present danger of delivering a premature baby that may not survive.[5,6]

It is recommended that a general surgeon have skilled obstetric consultation prior to performing a repeat section, in an attempt to ascertain the size of the baby.

It should be noted that if the repeat section rate had not increased so greatly, the over-all rate in the present study would have been 4.4 percent instead of 5.2 percent. This is an ever-burgeoning problem that will probably not cease. It can only be hoped that fewer damaged babies and mothers are the result.

It is commonly believed that if a fetus in breech presentations is delivered from below in a primipara, there is a high incidence of unavoidable complications such as those involving the umbilical cord. It is felt that cesarean section offers the baby the best chance for survival. This must be weighed against the fact that the mother is an "obstetric cripple" thereafter. If the incidence of section for this cause had remained the same in the last 6 years, the over-all rate would only have been lessened by 0.2 percent.

Another problem concerned with the indications for section is that of cephalopelvic disproportion. The Department of Obstetrics has ruled that all primigravidas should have a routine pelvicephalogram performed 10 to 14 days prior to the estimated date of confinement. In view of the current publicity regarding radiation exposure, I question the value of this as a routine procedure. I feel that the experienced obstetrician will be able to judge by palpation whether the pelvis is adequate and estimate the relative size of the fetus.

The question at many hospitals is complicated by the fact that general practitioners, perhaps without experience in evaluating the pelvis by palpation, perform deliveries. In general, they need the help of the radiologist to determine a disproportion or an abnormal fetal position.

It is of interest that the Department of Radiology at Metropolitan Hospital has devised a technic for pelvicephalography which materially reduces radiation exposure, in some cases by as much as 89 percent.[7]

Comparative study

Age and parity of patients • In this series of patients the ages varied from 15 to 43 years, the greatest number being 26 years old. Eleven primiparous patients were over 35 years of age.

Of the 277 sections performed, 158 were on multigravidae and 119 were on primiparae.

Types of procedure performed • Classical cesarean section was performed 118 times (42.6 percent), and low transverse cervical section was performed 159 times (57.4 percent). This is a change from the previous study in which 64 percent of the sections were of the classical type.

Tubal ligation was performed 21 times at section, myomectomy 3 times, lysis of adhesions twice, and umbilical herniorraphy and appendectomy once each. The latter procedure is not universally approved, but authority can be found for it.[8,9]

Maternal mortality and morbidity • There were no maternal deaths in this series. The average hospital stay was 7 days, varying from 5 to 22 days.

Complications are listed in Table III.

TABLE III—COMPLICATIONS

	No. cases
Incisional abscess	4
Incisional dehiscence	3
Lower nephron nephrosis due to:	
a. Transfusion reaction	1
b. Hemorrhage (abruptio placentae)	1
Ileus	2
Pyelitis	3
Diabetes	2
Eclampsia postpartum	1
Nephritis	1
Fistula from ileum requiring further operative treatment	1
Punctured bladder	1
Pneumonitis	1
Puerperal sepsis	1

Review of the previous study shows few of these complications. The increasing over-all incidence of hospital wound infection may account for the increased morbidity due to infection.

Fetal Mortality • The over-all fetal mortality in this series was 5.4 percent. The deaths which may be regarded as nonpreventable, that is, not attributable to the cesarean section, were as follows: Stillbirth oc-

curred in 5 cases of abruptio placentae, and 1 case of eclampsia. Neonatal death occurred in 1 infant with congenital anomalies incompatible with life and in 1 case of placenta previa. This yields a fetal mortality of 2.5 percent.

One baby died in the neonatal period, in the case where a previously sectioned uterus ruptured at 7 months gestation. Two babies died following prolonged labor, where section was necessary after high midplane arrest and failed forceps attempt. Another baby, a premature, died following an elective section for a breech presentation in a primigravida. This one case causes the death rate for this type of case to be 2.6 percent. It also shows in some small measure that cesarean section is not a 100 percent guarantee of a living child.

Two other deaths resulted from unknown causes: One case was in a repeat section, and in the other section was performed for psychiatric reasons.

The four cases (3 electively sectioned, without obvious causes of death, and the 1 ruptured uterus) are directly attributable to cesarean section, and yield a fetal mortality rate of 1.4 percent.

Another problem mentioned only briefly in the previous survey is prematurity. In this study, 17 babies were judged premature at birth because they weighed less than 5½ pounds. Of these 17, 7 were caused by errors in judgment as to the time of elective section:

Previous section, 4 prematures
Primigravida breech, 2 prematures
Cephalopelvic disproportion on x-ray, 1 premature.

Again I must stress the urgent need for keen obstetric judgment as to the time of section.

Another aspect of fetal mortality arising from cesarean section is in cases of hemorrhage, particularly abruptio placentae, and in prolonged labor. In surveying the literature, I rarely found any reference to the section that was performed *too late,* with resulting loss of a baby. Should not these cases be removed from the nonpreventable list and attributed to cesarean section? This is of necessity a philosophical question, difficult to document accurately for discussion. It does emphasize again the need for obstetric diagnosis and judgment, plus education for the general practitioner doing obstetrics as to the dangers of prolonged labor and the signs and symptoms of abruptio placentae.

Summary

In the past 6 years (1953 to 1958) 277 cesarean sections were performed in the course of 5,305 deliveries. This is a rate of 5.2 percent, which compares favorably with the rate reported from other institutions. The over-all rate from Metropolitan Hospital, including the figures of the previous study, shows that for the 12 years of 1947 to 1958 the cesarean section rate is 4.7 percent in 8,145 deliveries. The over-all fetal mortality rate is 5.4 percent.

During the period of the current study 17 premature infants were delivered, of which 7 are regarded as being avoidable through the exercise of better obstetric judgment.

A plea is made for more reliance by the obstetrician on his ability to determine by palpation pelvic capacity and fetal size.

Attention is drawn to the fact that repeat cesarean section has become the most prominent reason for section today, the incidence of this condition having increased from 16 percent in the prior study to 34 percent in this analysis.

Low transverse section has been utilized more frequently than classical section in the last 6 years. In the prior study nearly two thirds of sections were by the classical method.

It is also noted that fetal distress has entered the picture as a cause for section, which shows an increasing awareness of the state of the unborn child. In this connection, earlier section in cases of abruptio placentae and prolonged labor may produce more healthy babies.

It is felt that critical self-evaluation by each hospital staff of its cesarean section statistics will lead to a proper rate of sections which will be in the best interest of the mother and the child.

Medical Tower, 255 South 17th St.

Acknowledgment

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The incidence of dermatophyosis and potential treatment with griseofulvin*

A. P. ULBRICH, D.O., and T. H. BONINO, D.O., Detroit, Michigan

No therapeutic agent has had a more dramatic birth than griseofulvin.[1,2] Rumor that the substance was to be marketed caused excitement among interested laymen and physicians alike. Among these, no group was more cognizant of the need for such a preparation than dermatologists. There has long been speculation concerning some theoretic substance that would deter the infecting organism enough to allow the host—the nails, skin, or hair—to grow faster than the organism could invade. The eventual effect of such treatment would be desquamation of the infected area and resultant cure.

One author[3-5] gave this phenomenon of dermal growth the very suitable name of "epidermal effluvial current," describing how the production of keratin represents a sort of continuous flow. He pointed out that a fungus needs to grow at least as fast as the keratin in order to maintain its damaging effects; on the other hand, anything which is deleterious to the invading organism could slow its inward growth and determine the outcome of the battle.

Most fungous infections are self-limited by this physiologic mechanism of dermal growth; however, those which are not become problems because topical therapeutic agents used to date have been unable to penetrate the keratin of skin, hair, or nails where the parasite lives and multiplies. The ideal agent would work from within outward, in cooperation with keratin growth. Since griseofulvin apparently acts in this manner it has theoretic promise of great usefulness.

However, there is cause for concern, for a number of reasons. One is the frequent problem of misdiagnosis, making the possibility of prescribing this medication for the wrong condition very real. The illustrations included with this paper point out some of these possibilities for error, and other specific instances will be detailed later. In addition, the statistical study described herein shows that the indications for griseofulvin are actually quite few, and their occurrence is relatively rare.

It should be remembered that other agents have also shown great promise when first introduced; for example, oral undecylenic acid had a dramatic but brief period as the wonder drug for psoriasis. However, griseofulvin should not fall into the category of a relative hoax, for many reasons. Yet there are dangers of another kind: The public is subjected to so much insinuated and implied information through the lay press that patients come to the doctor almost demanding a certain medication. A few years ago it was phenol and camphor for athlete's foot. Last year it was the oxypsoralens for vitiligo. Will it be griseofulvin this year?

Some background on the evolution of this drug might be useful at this point. The discovery of

Fig. 1. Trichophyton rubrum on the dorsum of hand of bus driver, of many years' duration. This will respond to griseofulvin.

*Presented at the annual meeting of the American Osteopathic College of Dermatology, Chicago, July 14, 1959.

griseofulvin goes back to 1939, when Oxford, Raistrick, and Simonart[6] first isolated a metabolic product of a species of Penicillium and gave it that name. Another group of workers[7,8] later found a similar substance in another species of Penicillium, which caused stunting, branching, and distortion of the germ tubes of certain fungi and interfered with hyphal development. They termed this substance the "curling factor." It was later discovered that the two substances were very similar, if not identical.[9,10]

The first application of griseofulvin was in agriculture, since it was shown to prevent the hyphae of infecting fungi from penetrating the plant cell walls.[11] However, it was not applied in animals until 1958, when Gentles, Barnes, and Fantes[12] reported that experimental infection of guinea pigs with Microsporum canis and Trichophyton mentagrophytes had been successfully treated with oral griseofulvin.

The first report of successful treatment in man was presented in Vienna in November 1958.[13] Since then,

Fig. 2. Maceration of interdigital spaces from soap. This had been treated periodically for a year as "athlete's foot." Griseofulvin will have no effect.

a number of clinical studies both here and abroad have indicated the potential usefulness of the drug.

The actual mechanism of action is unknown, but it has been said to be recoverable unchanged from the keratin produced while persons are receiving it orally.[5] It would seem that its action is due to its incorporation in keratinous tissue,[12] perhaps by producing a barrier of keratin which stops the inward advance of certain fungal hyphae and which persists until outward growth eventually causes the infected epidermis to be shed.[5]

The real cause for concern is that this new drug might be used almost as a means for ruling out mycoses, because its indications are not understood. A microscope, a slide, and some potassium hydroxide are not enough to make a diagnosis; the finding of mycelium is suggestive of mycotic infection but not pathognomonic.[3] Even the finding of mycelium is not an indication for medication. For example, a pigmented area on the chest might readily demonstrate mycelium, yet Malassezia furfur, which causes pityriasis versicolor, is not affected by griseofulvin.

Fig. 3. Circinate lupus erythematosus of forehead, previously diagnosed as "ringworm." Griseofulvin would be of no value in this case; its use would further delay proper treatment.

I know of no diagnoses which are more acceptable to a patient and more abused by physicians than "ringworm" and "fungus." Part of the popularity of "fungus" may be a result of the frequent publicity given these disorders during World War II; another part is the advertising of preparations for self-treatment of supposed fungous diseases, particularly of the feet. External otitis has so long been accepted as otomycosis that patients become almost belligerent when it is suggested that they do not have "fungus in their ears." The excellent work of Perry[14] and Senturia[15] has shown that external otitis is almost invariably of bacterial origin, but somehow this information has not been disseminated through the medical profession.

Anyone who has worked with dermatophytes has been puzzled at the capricious character of the host sites. Why should one or more nails inhabiting the same environment and confined within such an ideal incubating chamber as a shoe be spared infection? It is almost exceptional, even with Trichophyton mentagrophytes or Trichophyton rubrum, when one or more toenails are not spared the infection for a matter of years. And why should such a transient

Fig. 4. Pityriasis rosea, most commonly misdiagnosed as a "ringworm." Griseofulvin would not affect the dissemination. The error would not long go unnoticed.

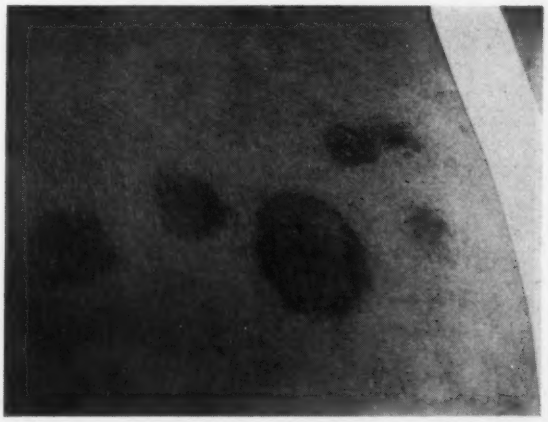

Fig. 5. Dermatitis venenata of toes from overtreatment of self-diagnosed and drug store-treated "athlete's foot." Griseofulvin is of no avail.

thing as freezing cause changes sufficient to make a favorable[1] environment for Trichophyton rubrum for years to come? The patient in Figure 6 is an example of this, although it can be seen that only the skin is affected while the nails show no change.

Work continues here and abroad on many of these factors.[16-18] Recently the use of tissue cultures has aided in better understanding of the fungiostatic effect of serum.[19,20] It must be determined what is the natural immunity of many individuals—for example, of children in the same classroom under almost constant exposure to tinea capitis, caused by Microsporum audouini, where it is rare to find the infection in over 5 per cent of individuals.[21]

Indications for griseofulvin at present are known to be in diseases caused by the Trichophyton, Epidermophyton, and Microsporum groups. This is because its action is to inhibit the mycelial phase.[5] This parallels its use in plants, where the absorption of griseofulvin through the roots prevents mycelial formation and by its fungistatic effect at least prevents the evidence of disease from being manifested. A sincere clinical suspicion would concern a progressive infection, of probably more than a month's duration, with positive evidence for mycelium on potassium hydroxide study. A culture should be taken, and the drug may be given.

Another candidate for the medication would be a child presenting positive Wood's light on a scalp lesion. Cultures should of course be taken, and simple potassium hydroxide study would amplify the findings. Both Microsporum audouini and Microsporum canis respond well. Apparently even the very difficult type of tinea capitis, that caused by Trichophyton tonsurans, will respond well to griseofulvin. We have not yet seen reports of treatment of Microsporum gypseum, but would suspect that it would be effective.

It is to be remembered that the drug is fungistatic and not fungicidal. Blank and Roth[1] noted that fungus pellets which had been suspended in griseofulvin for 14 days commenced normal growth when plated out. In a patient, the infection remains until the part is either removed or normal desquamation takes place.

Fig. 6. Trichophyton rubrum of the foot. This patient had one foot "frozen" in Korea. Only this foot was involved, and the disorder had been present for 5 years. Nails and other areas have never been involved. Griseofulvin will be effective, but recurrence is possible.

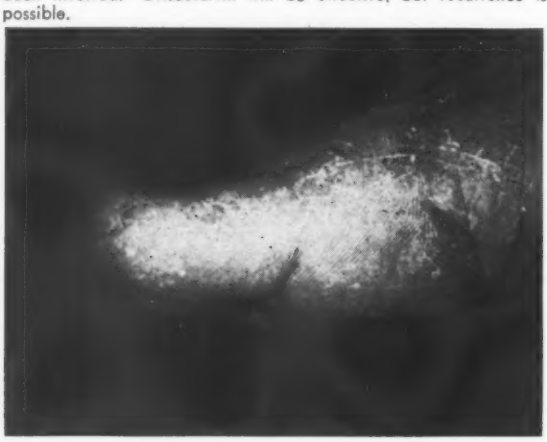

Fig. 7. Atypical psoriasis of the scalp with some temporary hair loss. Griseofulvin is not indicated.

The topical effect of the medication is controversial. Griseofulvin has no effect on the monilial infections; so an infection with Candida albicans (Monilia) could not be treated orally or topically. As previously mentioned, even though mycelia are profuse in Malassezia furfur (pityriasis versicolor), it is not treatable with griseofulvin. The deep mycoses, such as actinomycosis, blastomycosis, and histoplasmosis, are not responsive, nor are mycoses caused by the Sporotrichum and Hormodendrum groups.

Like many physicians with good intentions, we have kept a record of dermatophytes seen in our office, with the idea of "someday doing something with it." The real incidence of these diseases, as proved by laboratory culture, is surprisingly small.

Cultures were taken in all cases where there was even a remote clinical suspicion. Direct potassium hydroxide studies were done, but these findings were not the criteria for culture; rather, we were guided by clinical findings and our own index of suspicion. In the presence of fluorescence under Wood's light

Fig. 8. Circinate impetigo of the forehead and scalp, previously diagnosed as "ringworm." Griseofulvin would only delay proper treatment.

it was automatic. Identification of the organisms was made or confirmed by mycologists whose work is acknowledged at the close of this paper.

The over-all incidence of dermatophytes, as proved by laboratory culture, was surprisingly small in our area. Our practice is in metropolitan Detroit, and most patients come from within a radius of 10 miles. About half are referred as "problem cases" by other physicians. An average of 150 new patients are seen each month, or 1,800 a year. For a 5-year period, the incidence of proved mycotic infection was 2 per cent (1.93 per cent) of the total patients seen. If the cases of Microsporum audouini were eliminated, the incidence would be less than 1 per cent (0.91 per cent). Table I gives details of the study.

TABLE I—DERMATOPHYTES IN THE DETROIT AREA, 1954-1958

	1954	1955	1956	1957	1958
M. audouini	26	14	20	23	9
M. canis	1	..	1	1	4
M. gypseum	1	..	1	..	..
T. rubrum	2	6	6	2	5
T. mentagrophytes	3	9	10	13	7
T. tonsurans	1	1	1	..	..
T. verrucosum	..	1	..	..	..
T. sulfureum	1	..	..	..	..
E. floccosum	1	1	..	..	3
Totals	36	32	39	39	28
Total cultures taken	90	120	115	110	113

By way of comparison, a series of 1,000 consecutive cases seen in our office during 1956 had the following percentages of other disorders:

Hemangiomas	36 cases, 3.6 per cent
Pityriasis rosea	25 cases, 2.5 per cent
Malignancies of the skin of all types	13 cases, 1.3 per cent
Acne	27 cases, 2.7 per cent
Alopecia areata	8 cases, 0.8 per cent

This may only prove that we are extremely cautious in the diagnosis of "ringworm" of any type.

One other word of caution might be given. It is our opinion that an ungual infection of long standing will eventually change the character of the hyponychial area. With the resultant scarring, the nail can no longer adhere to its bed. There is also the factor of previous treatment, particularly on nail lesions. We have followed cases for several years, with repeated negative cultures, where the nail appeared detached and there seemed to be clinical evidence of onychomycosis. We came to feel that this represented fibrotic change in the hyponychial areas. Such lesions will not respond to griseofulvin.

The potential drug resistance is only to be mentioned, as it is just now being suggested in the literature.[22]

All of this would indicate that the number of cases where griseofulvin will be applicable as a treatment of choice is surprisingly small. The drug is not to be used empirically.

18820 Woodward Ave.

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The effectiveness of cytology centers in widespread cytologic diagnosis of cancer*

J. ERNEST AYRE, M.D.,† Miami, Florida

Major break-throughs have now enhanced the ability of today's physician to detect certain forms of cancer early enough to cure them, by applying the scientific technics of cytology. Additional minor break-throughs are occurring each year to enable earlier detection of cancer of the lung, throat, stomach, and prostate.

Cytodiagnosis • The greatest achievement relates to the ability of cervical cytology to detect uterine cancer as far as 10 years in advance of signs or symptoms, through a simple, painless, bloodless, cell-scraping procedure. The import of this break-through is so great that 53 million American women over the age of 20 should have cervical cytology tests, now considered the most effective guarantee against death from uterine cancer. The tragedy is that despite perfection of technic and method only 3 million of the 53 million American women over age 20 are receiving the protection of this remarkable test.

Second to the cervical test in simplicity and efficiency is the throat brush test and sputum cytodiagnosis for early detection of cancer of throat and lungs. Then follow tests for cancer of the prostate and stomach. Together, these constitute the five major forms of cancer ready for widespread cytologic testing in physicians' offices, to prevent cancer deaths.

An emergency situation in the practice of the healing arts exists today because of the lack of adequate facilities to screen the millions of cytology tests which should be processed without delay. Another emergency, according to the Cancer Cytology Foundation of America, is the result of the lack of trained cytologist screeners and professional personnel to carry the diagnostic load. Regional cytology centers will solve both problems by providing training, as well as cytodiagnostic facilities, to speedily widen the scope of cytologic diagnosis.

Dr. Homer Pearson, in an address before the American College of Pathologists, has indicated that to reach the 10 million annual test mark, cytologic testing should be increased both at the local level by hospitals and pathologists and in cytology centers and institutions specializing in cytodiagnosis, training, and research. To carry this minimal load would require seventy cytology centers each processing 100,000 tests annually, in addition to presently existing centers, hospital laboratories, and private laboratories of pathology. The establishment of adequate cytology programs presents a real challenge to the private practice of medicine, because if private medicine fails to fill this urgent need, state medicine or government sponsored programs will step in to fill the breach. The need for privately sponsored programs becomes even more urgent since U. S. Public Health Service research study programs in cytodiagnosis, such as that being conducted in Memphis, will be discontinued by the end of 1959. This is because they have completed the research and proved the value of cytology in cancer detection, and so Dr. Heller, Director of the National Cancer Institute, states that doctors everywhere should now perform vaginal smears on all patients seen in private practice.

Regional cytology centers • I would like to illustrate how effective a cytology center can become in screening and diagnosis for cancer by describing the experience of the Miami Cytology Center during the past 9 years. We apply the term "screening" to the cervical cytology test because this is the chief area where routine testing of all adult women has been advocated by leaders in preventive medicine. In other areas, such as the stomach and prostate, cytodiagnosis has been chiefly employed after the appearance of a danger signal. I will also describe the sim-

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†Director, Cancer Institute at Miami; Medical and Scientific Director, Cancer Cytology Foundation of America, New York.

ple throat brush test now being readied for screening tests on heavy smokers over the age of 40.

Mass cytology screening of the female population has been shown to be capable of controlling, even "stamping out," cervical cancer as a cause of death. One method of applying cytology to female population testing, the regional cytology center system, was established at the Miami Cancer Institute in 1951 as a pioneer program. Experimental studies concerned with the selection and development of practical, effective cytologic technics were initiated in 1939 at McGill University in Canada.

Sponsored by the Dade County Medical Association, the Miami regional cytology center offers the following advantages: (1) It is acceptable to physicians and is described by some as a boon to the private practice of medicine. (2) It provides experienced cytodiagnostic service on a low-cost, nonprofit basis within the reach of all economic classes, including free tests to charity groups. (3) It provides a continuous, permanent form of medical service, contrasted to government- or Foundation-sponsored projects classed as short- or long-term research. (4) It is believed that a diagnostic service for which a modest charge is made is more efficient and practical in actual application than a free state- or government-supported service.

The Miami Cytology Center is composed of a group of M.D. cytologists and cytotechnologists (screeners) devoting full time to cytologic diagnosis, training, and research. Approximately 1,000 to 1,500 cytology tests are processed each week. Most physicians mail cytology specimens to the Center in specially prepared envelopes, utilizing the glycerine mailing technic. The Center provides diagnostic reports within 48 to 72 hours. Biopsy and histologic confirmation is advised on all positive or suspicious cases, but the Center does not engage in histologic study; each hospital has facilities available to handle this phase of the program. Treatment of positive cases is carried out by private or hospital physicians rather than by physicians in the Center. The only treatment administered in the Cytology Center is made in the Division of Clinical Research, where studies are conducted on one group of patients showing precancerous cells or on another group of hopeless cancer patients, or in connection with experimentation in the search for causes and possible cures of cancer.

In order to present the diagnostic activities of the Cytology Center, I shall deal briefly with each of the five major areas where cytology provides significant diagnostic information. First, let us consider cancer of the throat and lung, because of their increasing incidence and the urgent need for improved methods of early detection.

Throat and lung cancer

Common factors in both types • Although throat and lung cancer vary in anatomic site of origin, necessitating differing surgical approaches in therapy, there is much in common between bronchogenic carcinoma and cancer of the larynx. Both arise from the same type of epithelial tissue, and they have a common etiologic relationship to excessive cigarette smoking, the most important factor in lung and throat cancer. While alcohol intake contributes to throat cancer, there is no evidence that it influences lung neoplasms.

Epidermoid lesions have the property of exfoliating tissue cells from neoplastic growth processes. The remarkable potential of this cytologic system of diagnosis is dependent upon the shedding of myriads of diagnostic malignant cells, even when lesions are in an extremely early stage of development. Indeed, a remarkable discovery has come from combined clinical and cytologic studies of the cervix in the revelation that to the naked eye the malignant epithelial tissue may appear normal, having an intact surface or in some cases simple red discoloration when the lesion has already progressed to a stage of early infiltration. This phenomenon of benign, innocent appearance of the tissues during the early years of development of the neoplasm accounts for the widespread concept held that "early" cancer is seldom visualized and that suddenly the physician is confronted with a massive ulcerating lesion whose curability was doubtful.

Lesions of the larynx are now being detected with a new throat brush technic (devised by the author) in a previsual stage similar to earlier findings commonly observed in the cervix in which surgical biopsy confirms the lesions as carcinoma in situ. Chronically inflamed, reddened patches on the vocal cords which appear innocent may harbor early carcinoma. Diagnosis depends finally upon surgical biopsy, but preliminary detection, utilizing the throat brush cytology test, is now of very practical value.

Symptomatology • The diagnosis of cancer of the larynx should be relatively simple because of the accessibility of the area. Its cardinal symptom, hoarseness, is one that the patient, his family, and his physician are aware of at an early stage. Yet delay in diagnosis is all too frequent because hoarseness and a "slight sore throat" are such common symptoms that they are too readily ignored. Persistent hoarseness or difficult and painful swallowing, chronic irritation and clearing of the throat, and the spitting up of blood, should not be neglected. Patient and physician carelessness lead to procrastination and the most tragic delays. But a number of other factors further delay the diagnosis of cancer of the larynx. If the patient is a heavy smoker or an alcoholic, mucosal inflammation is often so severe that routine examination even with a local anesthetic may be impossible and most certainly is incomplete.

Smoker's cough, with or without expectoration of a moderate amount of clear or colored sputum, should be an indication for regular medical examination by the family physician. To wait for the expectoration of blood in the sputum is to delay until the dangerous stage is reached. It would seem good wisdom and good preventive medicine for heavy smokers with cough to have a medical checkup and chest x-rays and cytology tests of the throat and lungs at regular intervals.

Cell collection technic • The new procedure includes the collection of a cell sample in mucus brushed or swept directly from the vocal cord area. The mechanical brushing procedure accomplishes two objectives: First, it provides an excellent sample of cells from the larynx; second, it provides a physical irritation to provoke a deeper than usual cough and expectoration of sputum which is used as the initial sample to be searched for cells from the lungs and bronchi. The technic is simple and the throat brush may be readily used by the medical practitioner, technician, or nurse in office or clinic. For use in detection no anesthetic is required. Indeed, it is undesirable since a better sputum specimen is collected after the cough following the physical irritation of the brush, sweeping up cells and mucus from the vocal cord area. The first sample of mucus, that containing the cells from the throat area, is prepared by expressing the mucus secretion directly from the bristles of the brush onto a glass slide. The second sample, the expectoration of sputum, is collected by spitting into a small bottle of 70 per cent alcohol immediately after the cough which follows the brushing of the throat. The cytologic analysis of these two specimens provides initial cell detection in the over-40 individual who is asymptomatic but who smokes cigarettes.

It is not to be inferred that the examination of a single sample of sputum is adequate to *rule out* the presence of cancer of the lung, but when cancer is present, even the first sputum test may be diagnostic. Indeed, it has been observed that in most instances, when neoplastic cells were found, they were seen in the first sputum specimen examined. Many investigators consider cytologic examination of sputum to be a valuable addition to the procedures for diagnosis of carcinoma of the lung, and feel that in comparing the use of sputum with that of bronchial secretions, sputum is more practical. Whenever initial suspicion is aroused by atypical cells in the first test, further diagnostic investigation, including x-ray study, is indicated. At least three samples of sputum should be collected in any case where there is clinical suspicion, doubtful x-ray findings, or atypical or suspicious cell findings noted in the first sputum specimen. (When sputum is scanty and suspicion exists, the use of an aerosol pump nebulizer will provide voluminous specimens in such selected cases.) Indeed, bronchoscopy and the further search of bronchial washings may frequently be indicated to establish diagnosis or to rule out malignancy in patients with profound pulmonary disease which may possibly be malignant.

Problems of establishing final diagnosis for early lung cancer • While it may be easy to establish lung cancer when the disease is advanced, the problem is more complex in the early stages, calling for effective use of all available diagnostic faculties. While both x-ray and cytology may be conclusive in advanced cancer, the radiographic findings may be doubtful during the earlier stages. It is in this stage where the combination of repeated cytology studies with careful x-ray studies should contribute to the detection of a higher percentage of cases of lung cancer suitable for surgical therapy.

Where initial suspicion of bronchogenic carcinoma is aroused by suggestive or doubtful x-ray findings and confirmed as malignant by supplementary diagnostic measures such as cytology, bronchoscopy, or surgical biopsy, no problem exists so far as diagnosis is concerned. The problem is one of surgical therapy, and the earlier detection has been made the higher the percentage of cases amenable to successful surgical treatment.

However, where initial suspicion is aroused by positive or suspicious cells in the sputum and where initial x-ray studies do not confirm the presence or localization of the lesion, there is a real problem in determining the origin of the suspicious or positive cells and confirming that the lesion is malignant. Repeated x-ray studies must be undertaken, bronchoscopic investigations must be made, and selective aspirations or brushings of mucus and cells must be made from each lung and from each large bronchus. While genuine problems to confirm the diagnosis and to localize the lesion exist with this sequence of events, the results of surgical therapy will be radically improved where cytology tests of the sputum are positive and the lesion is confirmed as cancer before the x-ray-evident stage of tumor development is reached.

Simplicity of detecting laryngeal cancer • The routine sweeping of vocal cords by the throat brush as a detection procedure is proving extremely encouraging. It appears that the blind sweeping up of mucus from this area will enable detection of this form of cancer when it is extremely early and amenable to successful treatment. Recent reports emphasize the innocent appearance of lesions of the vocal cords proved by surgical biopsy to be carcinoma in situ. One of the immediate problems of the otolaryngologist inspecting the throat from which malignant cells have been swept is the selection of the target lesion or area from which the cells were shed to provide accurate biopsy-findings. Not infrequently, as in the case report below, repeated biopsies may be required before the heart of the lesion is found, as not infrequently tissues reveal structures which may be diagnosed histologically as "precancerous."

Case 1 • The patient was a male, aged 57, who had been a heavy smoker of cigarettes for much of his life. He asked for a throat cancer test because he was worried about an attack of laryngitis and hoarseness he had suffered 6 months previously. His laryngitis at that time had been treated by administration of penicillin and painting the throat with iodine, following which the symptoms cleared up. However, in view of his fear of cancer he requested that a special test be made. The primary indication for the cytology throat test at the Cancer Institute at Miami was to allay his fears and give him peace of mind. This was on August 14, 1957.

The cytology test for the throat was reported as revealing "cells showing marked precancerous changes approaching carcinoma in situ." Following the surprise cytology findings the patient was promptly re-

ferred (August 25) for laryngoscopic examination. On initial inspection the consultant saw no evidence of cancer but observed three reddened areas on the vocal cords. He indicated that he would take repeated throat brush cell studies under direct vision for confirmation, as well as tissue biopsies from the reddened areas. The second cytology test confirmed the first, showing cells of probable malignant type. The first series of histologic studies (September 5, 1957) showed "acanthosis with marked cellular atypism." A rebiopsy was suggested by the examining pathologist, particularly of the right vocal cord, "since the precancerous changes suggested the possibility of malignancy nearby." The operative report of the second biopsy was dated February 25, 1958, and it described a cyst of the left vocal cord and early ulceration of the edge of the right vocal cord. (It is uncertain whether ulceration was the result of nonhealing from the first biopsy or was indicative of possible progression of the malignancy.)

This test case demonstrates the usefulness of routine throat brush cytology as a simple office detection procedure on heavy smokers. It demonstrates the ability of cytology to detect unsuspected preclinical cancer in the throat before the stage of signs and symptoms.

The patient was given x-ray therapy. Eighteen months later the patient's voice is normal and the cytology and clinical appearance of the throat and vocal cords appear normal. Office records are as follows: On May 21, 1958: "Laryngeal examination discloses no evidence of the lesion. The x-ray therapy has been highly successful." On July 2, 1958: "Normal vocal cords, no hoarseness present." On November 5, 1958, after laryngeal examination: "No evidence of any lesion. Normal vocal cords, excellent voice." There is every indication that the cure will be permanent. Follow-up cytology tests and laryngoscopic examinations will be made each year.

Results • Results on cytologic findings in the throat and oral cavity will be presented in a separate group from those of cancer of the lung. The cytology of sputum has been studied for many years and the over-all totals extend throughout the 9 years during which the Miami Cytology Center has been in existence. However, cytologic studies of the throat and oral cavity are very recent since this represents a new field of research and diagnostic activity.

In the Research Clinic of the Cancer Institute, cell brushings from the throat and oral cavity have recently been taken in a series of 571 tests on 497 patients. Positive cancer cell identification was made in 30 cases; of these, the lesions were confirmed as malignant in 18, while 3 cases showed negative pathologic findings for cancer. In one, the lesion was a polyp; in one, Hodgkins' disease was found; in a third case, normal tissue was found. Follow-up findings were not secured in 9 patients. Therefore, in cases diagnosed positive by cytology and having a histologic follow-up, the accuracy was 85 per cent. Of 21 cases diagnosed as suspicious cytologically, histologic confirmation of malignancy was made in 6, while 6 showed negative histologic findings for cancer and on 9 patients no follow-up information was available. The over-all accuracy of cytologic detection in patients showing suspicious and positive cytology (51 cases), of which 24 were verified as malignant by histologic confirmation and 9 showed negative pathologic findings, totaled 72.7 per cent confirmed malignant lesions.

Cytologic studies have been made on 2,223 pulmonary specimens at the Cancer Institute during the past 8 years. The relative accuracy of cytologic detection is reflected in the statistical analysis of the following group of 1,470 cases, of which 1,149 were diagnosed as negative (78.1 per cent), 158 as suspicious (10.8 per cent), and 163 as positive (11.1 per cent). In the follow-up it was noted that 73 were confirmed as cancer in 79 of the 163 positive cases who had histologic studies. Therefore, 92.4 per cent of cases followed up were confirmed, as compared to 82.4 per cent of the suspicious cases confirmed as cancer.

Screening the millions of cell samples from the throat and lungs of heavy cigarette smokers represents a staggering problem, yet a brilliant opportunity for great achievement to curb mortality from cancer in these areas. There is no doubt that all heavy cigarette smokers over the age of 45 would benefit appreciably by having an annual throat brush and sputum cytodiagnostic test. The cigarette habit seems so much a part of American life that the advice of physicians against smoking compared with cigarette company propaganda is like a gust of wind driving against a Florida hurricane. It is significant to note that increasing numbers of physicians are dropping the cigarette habit, and in New England as high as 50 per cent have stopped.

Next best to stopping the habit is to apply all proved medical and scientific tests to protect the individual from cancer death. Regional cytology centers represent the most effective system to process the millions of slides which should be taken on heavy cigarette smokers.

Cancer of the esophagus, stomach, and prostate

The rotating gastric brush is almost 100 per cent accurate in the diagnosis of esophageal cancer. Diagnosis of cancer of the stomach calls for expert use of all available diagnostic procedures of proved merit. Best results come from combined gastric brush and x-ray studies, which together yield accuracy approaching 90 per cent, while either one alone may vary in different hands between 70 and 80 per cent. The great advantage of the rotating gastric brush is its simplicity and speed since it is possible to get an excellent sample of cells from the stomach lining in 2 minutes. The procedure is harmless and entirely safe, as proved by several thousand tests in the hands of scores of operators.

Cytologic testing of the prostate is a diagnostic procedure of great merit which has not yet become widely accepted and applied. A statement by the Rochester University group, however, reveals its superior value as the best and simplest detection proce-

dure in *early* prostatic cancer. Digital examination reveals 23 per cent, cytology detection 84 per cent, punch biopsy 10 per cent, x-ray none, serum phosphatase 6 per cent, and open surgical biopsy 100 per cent.

The results of the Miami Institute roughly parallel those of the Rochester group with 82 per cent accuracy in 1,565 negative cases (21.4 per cent false negatives). But 88.5 per cent of cases cytologically positive and having confirmation by tissue diagnosis proved correct.

The problem is how to confirm early prostatic cancer cell findings. To wait for a clinical nodule for biopsy may represent dangerous or even fatal delay.

One promising phase of prostatic cytodiagnosis lies in the practice of administering estrogenic hormones to elderly males who show cytologic signs of premalignant or carcinoma-in-situ stage neoplasms. In many of these the disease is prevented from progressing to a dangerous stage during the balance of life.

Uterine cancer

Cytologic testing • The cervical scrapings test provides an extremely sensitive and accurate cancer test detecting up to one third more early cancer than vaginal aspiration smears. It has also proved highly reliable in indicating the absence of cancer and thus in relieving cancer fear when the test is negative. At the Miami Cytology Center a 9-year program of cytology testing, by more than 1,524 physicians and 9 hospitals, has shown that approximately 1 per cent of cervical cancers have been missed (false negative) by the cervical scrapings test in a consecutive series of 231,789 specimens, in which 2,441 cancers of all types were detected. A total of 66 cancers were missed (2.6 per cent), including cervical and ovarian cancer, adenocarcinoma, and so forth. However, 2,376 cervical cancers were detected as compared to only 24 missed. So in the routine detection of cervical cancer in asymptomatic women, the cervical scrapings test with a wooden spatula is 99 per cent accurate.

The cervical scrapings test can detect routinely the 100 per cent surgically curable stage of cervix cancer designated as "carcinoma in situ." The test is so sensitive that repeat cell studies in completely healthy tissues need only be made at 2-year intervals. Even so, an annual cancer check-up with cytology is advised because the cervical test provides the excuse for many women to visit their physicians for an annual cancer examination to include breast, rectum, and other common cancer sites.

Problems of mass testing • One of the greatest opportunities in preventive medicine lies in the establishment of regional cytology centers and expanded laboratories of cytopathology as advocated by the Cancer Cytology Foundation of America.‡ Such centers will enable the processing of cervical cytology tests on a large proportion of the 53 million women over age 20 in the United States, to bring this common form of female cancer almost completely under control.

The cervical scrapings test is a simple, 2-minute, painless, bloodless procedure which can be taken in the medical practitioner's office for mailing to the cytology center or laboratory of pathology. It permits the detection of cancer when the cervical tissues appear benign, inflammatory, or completely normal. The problem under these conditions is to secure accurate histologic confirmation. We recommend that in the absence of a target lesion a ring biopsy with multiple tissue sections from the four quadrants be made. When tissue search is adequate the correlation between properly interpreted cytologic findings of early cancer and histologic carcinoma exceeds 98 per cent.

Encouragement of the masses of women to visit their doctors to secure the protection of this simple but effective test calls for professional and public educational and publicity programs, including press, radio, and television. To reach young women, tests should be taken routinely during pregnancy since this physiologic state inevitably brings the patient to the examining physician. Contrary to early reports it is of prime importance that cervical cytology tests be taken during and after pregnancy. Positive cytology in pregnancy usually indicates the presence of cancer which may be confirmed and, when preclinical, treated curatively in the postpartum period. Successful ring biopsy is now commonly practiced during pregnancy without ill effects.

Cytology training centers

Cytology centers represent an ideal training ground for urgently needed technical and professional personnel. A serious drawback in most medical schools is the shortage of cytologists and pathologists trained in cytology, to provide regular and effective courses of training in cytodiagnosis. The cytology center, with experienced teachers and technical instructors, utilize the great volume of positive and negative cytologic material to provide effective training for new doctors and screeners wishing to become specialists in this scientific field.

There is no doubt but that hundreds of screeners and scores of physician-cytologists are needed for volume work, but immediate emphasis should be placed upon providing urgently needed trained cytotechnologists to aid the overloaded cytologist and cytopathologist. Young women interested in medicine are provided with a brilliant new career with an assured future in a rapidly expanding specialty where there is practically unlimited demand for her services.

The scarcity of trained personnel should not be an excuse for relaxing every effort to apply cytology as widely as possible, as quickly as possible, but to accelerate this practical application of the method it is imperative that the tempo of training programs be stepped up and that more young people, both men and women, be attracted into this challenging new field where so much service can be rendered in medical and professional work without the prolonged training necessary to secure a medical degree.

‡Cancer Cytology Foundation of America, Inc., New York Academy of Medicine Building, New York City.

In the past the lack of expertly trained personnel has greatly retarded the proper utilization of cytology as a detection procedure in the hands of the family doctor. But in future years the need for trained technical personnel will be even greater.

A recent survey made by the National Health Institute of the U. S. Public Health Service indicated that 50 per cent more persons will be stricken by cancer in this country during the next 25 years. At the present time, 500,000 new cancer cases are being diagnosed yearly, and that number is predicted to climb to 750,000 annually by 1975.

Conclusions

Mass cytology screening programs in the past have been concerned largely with testing vaginal and cervical smears for uterine cancer. This still represents a revolutionary procedure now proved capable of detecting the common lesion, cervical cancer, years before the danger signal stage. The method is so efficient and simple that death from this malignant disease could be eliminated entirely by establishment of cytology centers to bring this cancer protective test to all adult women.

Recent advances in the detection of cancer of the throat and lungs, and improved technical procedures for the prostate and stomach, signify that five major forms of cancer are now ready for the widespread application of cytology in the hands of the practicing physician to help stamp out cancer death.

An emergency exists in medicine to train technical personnel (screeners) and professional cytologists to extend widely the use of cytology as a health measure.

Tens of thousands of lives may be saved from cancer today through early cytologic diagnosis without having to wait for any new discovery of cause or cure. Research must go on, to solve the major problems of cancer. But early diagnosis in the hands of the practicing physician, utilizing regional cytology centers, provides today's best hope for successful management and control of cancer. Prompt diagnosis before the stage of suspicion, and institution of proved treatment methods (radium, x-ray, and surgery), offer very substantial gains in cure rates.

Cancer Cytology Foundation of America, Inc., Florida Division
1700 Biscayne Boulevard, Miami, Florida

Accidental hypothermia complicated by bronchopneumonia Report of a case

M. J. ANDERSON, JR., B.S., D.O., Chicago, Illinois*

This case is reported because the number of cases of accidental hypothermia is relatively small. It is hoped that through the correlation of clinical observations of such cases with the results of animal experiments and physiologic principles, a more effective management of severe hypothermia may be obtained.

A 32-year-old white woman was admitted to the Chicago Osteopathic Hospital in a comatose state with no visible signs of life other than a shallow apneustic respiration every 15 to 20 seconds. The skin had a marked pallor and was very cold. The pupils were widely dilated and nonresponsive to light, and there was no retinopathy. Both nares were encrusted with mucus, and the lips and oral mucosa were dry and had a parched appearance. The tympanic membranes were gray and intact. There was no evidence of trauma or skin lesions other than areas of ecchymosis at the inferior angle of the right scapula and over the right lateral gluteal area.

A blood pressure reading could not be obtained and arterial pulsations were not elicited. Evidence of cardiac activity was obtained by auscultation over the lower sternal area and by an electrocardiogram which showed a sinus bradycardia of 28 beats per minute. The lungs were dull to percussion. Auscultation of the lungs was not satisfactory due to the bradypnea. There were no abdominal masses or ascites. There was no lymphadenopathy or peripheral edema. The limbs were flaccid and the patient was completely areflexic.

*Dr. Anderson is a resident in the Department of Medicine, Chicago Osteopathic Hospital, of which Ward E. Perrin, D.O., is chairman.

The patient had been found in her apartment with the windows open and the heat turned off. The outside temperature had dropped to 8 F. the preceding night. Several empty bottles used for barbiturates and other sedatives were found in the apartment. It was stated that the patient had in the past taken an overdose of barbiturates, and that she had recently been disturbed because of business problems. It was also learned that she had experienced two grand mal type of seizures in the past month. As far as could be ascertained, she had last been seen by others 4 days prior to admission, at which time she complained of a slight cough and head cold.

The patient was intubated and the Morch respirator was used (there was no laryngeal reflex). Nikethamide (Coramine), methozamine hydrochloride (Vasoxyl), and 5 per cent glucose in water were given intravenously without difficulty. A venous cutdown was done later, however, because of some difficulty in keeping a vein open. Auscultation of the chest now revealed coarse inspiratory and expiratory rales over the left lower lung field and the breath sounds were decreased over the right lower lung field. The stomach was lavaged because of the possibility of excessive barbiturate ingestion and the patient was covered with only a sheet so as to allow her to reach room temperature.

Adrenal cortical extract, tetracycline, vitamin B complex, and ascorbic acid were given intravenously. Nikethamide was given every 30 minutes and osteopathic manipulation (rib raising) every 2 hours.

Two hours after admission the rectal temperature was 19 C. (66.5 F.). At this time a radial pulse was barely palpable, and the apical rate was 38 per minute. After 3½ hours after admission, the temperature had climbed to 23 C. (73.4 F.); by 5½ hours it was 25 C (77 F.); and at 8 hours it was 26 C. (78.8 F.). Ten hours after admission the patient had very shallow active respirations at 16 per minute. The temperature was 29 C. An oscillatory systolic blood pressure was obtained at 60 mm. Hg. Auscultatory blood pressure could not be obtained. The urinary output up to this time was 300 cc., although the patient had received 2,000 cc. of fluid intravenously. The respirator was stopped and respirations were assisted with manual compression of a rubber breathing bag.

Fourteen hours after admission the temperature was 31 C. (87.8 F.). The apical rate was 72, and blood pressure was 76. The respirations became more shallow at this time and were coupled. Use of the respirator was begun again. At 16 hours the temperature was 31.8 C. (89.2 F.). At 17 hours the blood pressure dropped to 30; the apical rate was 100 per minute; and active respirations had ceased. Cedilanid-D and levarterenol (Levophed) were given without response. Eighteen hours after admission the blood pressure could not be elicited and there was no evidence of cardiac activity on the electrocardiogram. The patient was pronounced dead.

Admission laboratory findings were as follows:

Erythrocytes, 5,350,000; hematocrit reading, 50 per cent; leukocytes, 9,050, with 80 per cent segmented neutrophils and 20 per cent lymphocytes; nonprotein nitrogen, 64 mg. per 100 cc.; and carbon dioxide combining power, 9.1 mEq./l. (20 volumes per cent). Urinalysis showed a specific gravity of 1.016; albumin trace; sugar trace; leukocytes 4 to 6 per high-power field; and erythrocytes, 8 to 10 per high-power field.

Gastric washings were positive for barbiturates but the exact amount could not be determined because the dilution factor was not known. Serum was negative for barbiturates. A tracheal culture contained staphylococci, coagulase-positive.

An autopsy was performed by Dr. Morris R. Osattin. The anatomic diagnosis was: Diffuse bronchopneumonia of 5 to 7 days standing; right pleural effusion; right heart failure; and ependymoma of the third ventricle (small and probably asymptomatic).

On reviewing the history of this case it is felt that there were three possible sequences of events which led to her moribund condition: First, an overwhelming toxicity due to her pre-existing pneumonia with resulting coma; second, a grand mal seizure with following somnolence; and third, an overdose of barbiturates.

The absence of barbiturates in the serum would disfavor the third possibility although it is possible that the barbiturates were metabolized during the early part of her coma. Unfortunately, the urine could not be checked for breakdown products of barbiturate metabolism since the bladder was empty on admission. It is unlikely that the second course of events led to her condition since shivering probably would not have been prevented; the increased oxygen demand of shivering in conjunction with pneumonia probably would have caused an earlier death. Therefore, the first possibility is favored. The patient may have had a fever which prompted her to turn off the heat in her apartment and open the windows. Then the toxicity of her infection lead to coma which was deep enough to prevent shivering as the room temperature dropped.

Chicago Osteopathic Hospital
5200 S. Ellis Ave.

The medical management of this case was directed by Drs. Perrin and W. R. Patterson.

EDITORIALS

THE JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION

This periodical is the official publication of the American Osteopathic Association.

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As it should be everywhere

When a three-alarm explosion and flash fire occurs in a hospital it is special drama, even in a hospital's drama-packed routines. If the incident occurs midway in a week of hospital dedication activities, if it is related to a $2½ million expansion and remodeling program and prefaced 10 days before by an emergency patient evacuation and Fire Control Institute —that combination of circumstances is news of such special flavor as to challenge reporters. And so it did, those of the staffs of Columbus, Ohio, newspapers that reported the happenings that overtook Doctors Hospital on November 12, 1959—a $75,000 disaster, potentially tragic but ending without tragedy.

There is not only news in the incident; there are lessons in management that call for editorial comment directed to all osteopathic hospitals. Readers should read the full Doctors Hospital story in the February FORUM. It uncovers a situation that should obtain wherever there is an osteopathic hospital. Authentic hospitals are *community* affairs, public or private, osteopathic or medical, regardless of their classification. These institutions by their very nature are a part of the total community. If they act so, the community will recognize the fact and respond in turn. Doctors Hospital, Columbus, Ohio, by every standard is an authentic institution.

Doctors Hospital (unmistakably identified in Ohio's capital city as an osteopathic institution approved by the American Osteopathic Association) did not need so dramatic an event as a serious fire to set forth its status in metropolitan Columbus as a medical teaching center of high rank. The publicity inevitable to the disaster, however, showed the hospital's status to be accepted by the entire community. This is the significance to which THE JOURNAL points. This is recognition "as it should be everywhere": total community acknowledgment of the role of an osteopathic institution as one of the units ministering to the welfare of an expanding community.

It should be known that the Columbus Doctors Hospital has never asked for special privileges, claimed unusual merit, played up unusual differences in hospital services, or pointed to its unique contribution to medical care. Although the hospital does make a unique contribution to the community, it is an osteopathic institution.

Striking leadership in medical care to the community has been afforded to Columbus citizens through the Columbus Hospital Federation in which Doctors Hospital is an active member. Officials of the Hospital speak emphatically of their indebtedness to the Federation for the vision of its past and present leaders. It is true they have shown no special favor to the osteopathic institution. But as a hospital federation dedicated to the welfare of the community, it has recognized that in its welfare were involved three major building programs of Doctors Hospital itself. Osteopathic institutions ask only for fair dealing.

From its beginning the hospital has frankly admitted its dependence upon organizations and people. It has made every effort to render a superior service to the community without claiming to do so. This is the basis upon which in 2 decades, a 24-bed hospital grew into a 225-bed institution. Although osteopathic institutions were unknown in the Columbus area previous to 1940, when Doctors Hospital was founded, within 4 years the capital city's single osteopathic institution was operating over capacity. In 1944 Doctors Hospital was forced to add 64 new beds; the project was begun and completed within the year. By then Columbus hospitals generally were forced to face the pressures of urban sprawl and in 1950 united cooperatively with each other

and the entire community to solve their expansion problems. Its community worth unquestioned, Doctors Hospital was included in a major investigation of the needs of metropolitan Columbus hospitals, and was among the ten hospitals participating in the first United Hospital Campaign in Columbus. For Doctors Hospital the practical results were an 86-bed south wing and a surgery floor.

By 1956 crowded conditions again sharply hampered hospital services in Columbus. A United Hospital Building Fund yielded $8,000,000 in gifts through the farsightedness of the areas' business and industry and the generosity of its citizens. The Fund's success was a prelude to the passage by Franklin County (Columbus is its county seat) voters of a $15 million hospital bond issue needed to finance the expansion of the community's hospitals. Thus the combined efforts of industry, individual citizens, and voters harvested $23 million for metropolitan hospital facilities.

Through this unique community program Doctors Hospital had been able to complete its new $1 million wing, had remodeled its old building, and had just merged the two into one beautiful, functioning unit at a total cost of $2,486,742. Then came the fire!

Dedication of the new structure was set for Sunday, November 15, 1959, but on Thursday, November 12, as detailed in the February FORUM, occurred that near-tragic happening, the flash-fire. The dedication ceremony has been postponed until the latter part of January.

Although the disaster has slowed up Doctors Hospital's opportunity to give its widest possible service, it must have convinced any doubting Columbus citizens of the concerted greatness of their community. The quick and efficient action by hospital personnel, the responsibility of construction workmen, and the speedy and thorough response of the Columbus Fire Department to the three-alarm call that resulted in controlling the blaze within 27 minutes after the first alarm—these are the bases for strong editorial commendation by the *Columbus Evening Dispatch*, headed "Speedy Action Averts Disaster." The editorial went further and pointed to the incident as illustrating "the importance of preconceived plans to meet disaster situations of all kinds."

Seen in this short perspective, the disaster response illustrates the worth of preconceived plans not only to meet disaster but to meet human needs that require organized human service. Doctors Hospital, in breadth of management, in long-time conception of its true place in the community, in its true willingness to cooperate with welfare projects other than its own, and its own forehandedness in relation to disaster—all of this is as it should be for every osteopathic hospital, large or small, in the United States.

The Columbus osteopathic situation has set new standards of every type for what should obtain in all of our profession's institutions, from the largest to the smallest. Too few have attained such a status community-wise. For those to whom the Columbus situation seems an ideal, Doctors Hospital leaders would doubtless say, "This we did not gain in a day!" And yet so fine a story as this prompts THE JOURNAL to insist: "This is as it could be almost everywhere."

Awards to journalists

In an attempt to encourage journalists to report accurately the status of osteopathic medicine as it relates to the health needs of the nation, the American Osteopathic Association 2 years ago set up three annual awards of $100 each for outstanding newspaper stories about osteopathy. This issue of THE JOURNAL carries the announcement of awards to be made in 1960 for material published during 1959. The announcement gives full details concerning the rules, procedures, and methods of judging.

Many D.O.'s have yet to learn of these competitive awards and thereby have failed to pass on this information to their own newspaper or newspapers—newspapers whose editors could be interested in encouraging their writers to report the osteopathic story accurately. Doctors are the ones most likely to see material about osteopathy published in local newspapers. They are likely to know both the publisher and author and to be in a position to suggest that the article be entered in the American Osteopathic Association's 1960 newspaper story competition.

Where local newspapers have published no articles or news stories about osteopathic medicine in 1959 worthy of submission for the award, where osteopathy has been adversely reported, or where osteopathic physicians are not considered as playing a part in the health care of the community, it would be a positive move to secure better osteopathic reporting if the local doctor would give editors a copy of the announcement of the 1960 A.O.A. annual awards. Facts change minds. Accurate source material about the osteopathic movement in medicine is difficult to find except as made available through doctors of osteopathy.

The announcement on page 70 of the December FORUM can be used as tearsheets to give to newspaper editors. Also, the Division of Public and Professional Welfare of the American Osteopathic Association will send on request extra copies of the Rules and Procedures of the Newspaper Story Competition. Editors should be told that this is the third year for the contest and that the first two competitions aroused interest among writers. THE JOURNAL will be glad to furnish names of persons and newspapers receiving previous awards.

Today, osteopathy has a good press wherever journalists are truly informed about the profession. The offensive, inaccurate story originates in ignorance, not malice. Unfortunately, some doctors of osteopathy take *personal* affront at a story that does not reflect the true image of the profession's physicians or that casts osteopathy in a false light. Their pride hurt, these doctors write sharp letters to editors accusing them of being prejudiced and their newspaper of distorting the truth. Then the fat *is* in the fire! Rarely, however, do such stories originate in

prejudice. Almost always they are based on misinformation or lack of full information upon the author's part. Newspaper Story Competition is designed to encourage journalists to find authentic sources of material about osteopathy. It is a method of education about the role of osteopathy in meeting health needs. To be effective, however, the contest needs to be much more widely publicized.

The third year for awards will show greatly increased interest if each D.O. will see that full information about the contest is made available to newspaper editors in his community. In many places district and local osteopathic societies would be well advised to contact the newspapers officially, asking that notice of the awards be passed on to journalists. The newspaper story competition is potentiality unlimited for getting the osteopathic story better known. The success of such ventures—actually they are osteopathic development—hinges entirely on the local D.O. He has the key!

Annual congress on medical education and licensure

MILTON McKAY, General Counsel, American Osteopathic Association

The American Medical Association, in conjunction with the Federation of Medical Boards of the United States and other interested organizations in the fields of medical education and licensure, will hold at the Palmer House in Chicago, on February 7-9, the Fifty-Sixth Annual Congress on Medical Education and Licensure. For many years doctors of osteopathy serving on state medical boards have been attending the Annual Congress, but it was not until last year that a significant number of members of state boards of osteopathic examiners took advantage of attending this most informative educational meeting. Attendance is open to all licensed physicians and persons interested in medical education and licensure.

The American Osteopathic Association has long favored the maintenance of boards of osteopathic examination as the state governmental mechanism for the licensing of doctors of osteopathy. Administering these independent state osteopathic practice acts places upon the members of the osteopathic profession a responsibility equal to that which is placed by state law upon doctors of medicine administering separate and independent medical board acts. And this responsibility becomes greater with the almost complete recognition of the unlimited character of osteopathic education and practice throughout the country. If this responsibility is to be thoroughly exercised the D.O.'s must keep themselves educated and informed concerning all of the various aspects and ramifications of the education and licensure of physicians.

It is difficult for board members to keep abreast of developments in medical education and licensure merely by reading or studying publications in the field. Experience shows that one of the most fruitful means of keeping cognizant of new advances as well as basic matters relating to medical education and licensure is attendance at the Annual Congress. It is suggested therefore, that all D.O.'s concerned with education and licensure make arrangements, if possible, to be present at the Annual Congress this year.

A state-level need

Osteopathy is no longer a profession manned by D.O.'s alone. Its varied assistants are legion. The tremendous increase in osteopathic hospitals has attracted to it individuals whose first call is to assist doctors of osteopathy and their institutions in rendering a service to people in need of health care. These assistants are found in doctors' offices, group clinics, and osteopathic hospitals. Many are career people.

Michigan is one of the two osteopathically populous states where osteopathic medical assistants have felt the need to join together into an organization. The January FORUM reports on the rapid growth of the Michigan Osteopathic Medical Assistants Association. Although it was not organized until October 1958 it had a membership of more than 300 in October 1959. Ten local groups make up the state society. Additional groups are in the process of organization.

The Michigan group is made up of secretaries, receptionists, clinical laboratory technicians of every type, x-ray technicians, record librarians, office assistants, and nurses. Many are highly trained, proud of their professionalism, and keenly conscious that they are one with others similarly trained and experienced. But they occasionally find that employment under osteopathic auspices is a self-segregating thing. They are conscious that they are out of touch with colleagues in similar careers. If they belong to a technical society they may find renewal of membership denied them. For example, x-ray technicians are often warned that they cannot continue to qualify for membership in their society if they work for osteopathic institutions or doctors. These assistants need a sense of belonging, and they require organization if they are to possess power and influence.

The Michigan Osteopathic Medical Assistants Association has proved so useful that the suggestion was made at the October meeting of its executive board that a national body be gotten under way. There is no quesion that as soon as practical a national association of osteopathic medical assistants should be formed. It seems wise, however, that the Michigan group decided not to attempt to push for a national organization until assistants are organized in more states.

California also has an Osteopathic Medical Assistants Association. THE JOURNAL, however, has no up-to-date information on the size of the California group or the scope of its activities. The November 1959 issue of *The California Clinician* reported on meetings of three California chapters. A group of

medical assistants under osteopathic auspices was recently reported as having organized in Ohio.

It would be most useful in states where there are assistants' associations if their officers would write THE FORUM and thereby inform the profession of their activities. What is the situation now within Ohio groups? Are there groups organized in other states?

THE JOURNAL suggests that in states where assistants have no organization an attempt be made first to form a local chapter. A single chapter can serve as a nucleus and mark the beginning of a state association there.

Let it be known throughout a state that there is a going group of osteopathic medical assistants, and persons will make themselves known. They in turn may form units for their communities. Every hospital in a state could readily produce an organizational center for a chapter.

Assistants interested in forming an Association should write Georgia Garrison, secretary, Michigan Osteopathic Medical Assistants Association, 1209 Sydenham Street, Albion, Michigan. She has been highly successful in developing the Michigan group.

Osteopathic assistants have everything to gain by such a venture—and nothing to lose. Doctors of osteopathy and hospital administrators will find an organized body of technical assistants a factor in increasing the morale of those who work with them. Organized osteopathy in all of its varied aspects should lend strong support to these assistants. There are no valid reasons why hospitals should fear organization of their personnel. Assistants need to feel that they are a part of over-all organized osteopathy. They are an integral part of the profession.

The American Osteopathic Association strongly supports both Michigan and California osteopathic medical assistants in their development of strong state societies. At the right time it will welcome formation of a national group. THE FORUM is ready to report the news of all these activities.

If this comment uncovers local or state organizations of medical assistants that are unknown to the A.O.A. Central Office, please write THE FORUM giving full organizational details. Let us get acquainted all over the country.

The Educational Supplement

With this issue the Educational Supplement to THE JOURNAL becomes a 12-year old document kept current annually. Prepared by the Director of the Office of Education, Lawrence W. Mills, the Supplement is distributed widely within the profession since it is actually an official report. Distribution outside the profession, largely by request, is made to preprofessional advisors, college deans, vocational guidance counselors of secondary schools, college officials, and administrative officers of other educational groups. The annual Educational Supplement is the best single reference source for all persons who need to be informed about the educational training of the physician and surgeon, D.O.

Doctors of osteopathy should distribute it much more widely than they do among leaders in their communities who are not informed about the osteopathic physician's training. Reprints are available from the Office of Education of the American Osteopathic Association, 212 East Ohio Street, Chicago 11, Illinois.

1960 Yearbook and Directory

The fifty-second edition of the A.O.A. DIRECTORY is scheduled for mailing this month. Members of the Association will appreciate this earlier distribution, an innovation which will bring information more currently to its users than did the previous April distribution.

Although its size and shape have not been greatly altered, there are changes in the make-up of the 1960 YEARBOOK AND DIRECTORY which are expected to meet with wide approval. These changes have been made for one purpose—to provide a more efficient reference tool. On the one hand the material has been condensed for greater clarity; on the other, more information has been provided, especially on the education and practice of individual doctors. The system of coding, used in the member and nonmember geographic listings and explained in a detailed Key to Symbols in the editorial section, has been considerably amplified. A brightly colored bookmark carrying the coding system in shortened form is a new feature.

The Constitution, By-Laws, and Code of Ethics of the Association have been placed in an appendix where they will be more readily accessible for consultation. The index occupies the last two pages of the book, and a table of contents is provided. Many changes have been made in type style, all in the interest of fast reading.

In its new form and for its excellence, the DIRECTORY is indebted to many, not only to every Headquarters department but to consultants in layout and type design and to its printers. The man hours accumulated in the preparation of this indispensable reference work are always considerable, especially as they concern the listings of both members and nonmembers of the Association, and this responsibility is totally that of the Membership Department. The extensive alteration in form and style of the Directory's introductory material has made the production of the fifty-second edition a major editorial project.

The progress of the profession is again evident statistically. The DIRECTORY lists a total of 13,708 osteopathic physicians. Of these 10,484 are members of the American Osteopathic Association. The remaining 3,224 are nonmembers of the profession's national body but 1,217 of them are members of their respective divisional societies.

California continues to lead with the largest number of A.O.A. members, 1,978; Michigan is second with 1,456; Pennsylvania records 994; Missouri has a total of 850; and Ohio has 735.

The total osteopathic population by states is also led by California with a total of 2,470, Michigan

ranks second with 1,566, Pennsylvania third with 1,357, and Missouri follows with 1,157.

The YEARBOOK AND DIRECTORY is found valuable by many groups. It is widely distributed upon request to hospital insurance groups, life insurance companies, state and licensing boards, many industries, and such federal agencies as the Veterans Administration and various bureaus of the Department of Health, Education, and Welfare.

The effort to make the fifthy-second edition of the YEARBOOK AND DIRECTORY the most effective reference tool thus far will be well spent if it finds wider usage at less cost of time to the user. In itself, the 1960 YEARBOOK AND DIRECTORY of the American Osteopathic Association marks a new height in the growth of the profession it mirrors.

Live poliovirus vaccine

What is the current status of live poliovirus vaccine? More and more laymen are asking their physicians—Why not use oral vaccine?

THE JOURNAL in a November 1959 comment on Sabin vaccine reported its use almost world-wide, except in America. Dr. Albert Bruce Sabin did much of the basic work on an oral vaccine for polio and has been highly instrumental in its development. An official statement on oral vaccine has been recently released by the Public Health Service.

Doctors generally know that the attenuated live viruses used in the manufacture of these vaccines have lost the power to produce disease. The principal problem in evaluating the ultimate safety of live poliovirus vaccine is the possibility of the spread of the virus, by natural means from those vaccinated to others, coupled with its potentiality for reversion to virulence.

In June 1958, the Public Health Service established a committee on live poliovirus vaccine, composed of experts in the fields of virology and immunology from within and outside the government. The committee states that important progress has been made in the development of a safe and effective oral vaccine but it feels that some important safeguards will need to be developed before there can be full assurance of the safety and potency of the vaccine for general use by physicians.

The legal responsibilities of the Public Health Service for the licensing of biological products are far reaching. Not until it is satisfied that such manufacturing safeguards are established will the Public Health Service act on applications for the licensing of live poliovirus vaccine.

It is the duty of doctors to acquaint their patients with these facts and urge full use of the demonstratedly effective Salk vaccine. Its use is dangerously minimal even among children.

In briefer form

Physicians are asked to cooperate with the Committee for Research on Problems Associated with Blindness which is exploring means of disseminating occupational information to blind and partially seeing persons interested in professional careers. It is the hope of Committee members to produce recorded material based on interviews with blind and partially seeing persons who have already succeeded in various professions, and they need help in identifying potential interviewers. For their purpose the Committee is using the vocational habilitation definition of blindness, that is, that vision does not exceed 20/200 in the better eye with the best correction or vision with a visual field of not more than 20 degrees. For further information write Vernon L. Hull at 3003 Parkwood Avenue, Richmond 21, Virginia. ¶Dr. H. van Zile Hyde, Assistant to the Surgeon General for International Affairs, was recently appointed Chief of the Division of International Health. Dr. Hyde gave the keynote address at the Fifty-Ninth Annual Convention of the American Osteopathic Association in Los Angeles. Still timely and worth rereading, the published address, "The Health of the World," will be found in the October, 1955, JOURNAL. ¶The latest edition of the booklet, "Immunization Information for International Travel," is now available. It should be on file in every physician's office. For a copy write the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., and enclose thirty cents. ¶Dr. M. H. Simmers, now professor of surgery and pathology and coordinator of cancer training at the College of Osteopathic Physicians and Surgeons, Los Angeles, is one of the four authors of an article recently published in the *Journal of the National Cancer Institute*. The article, "Tumors Associated With Embedded Polymers," reports a study made of the long-term tissue effects of implantation of certain polymers in the tissues of laboratory animals. Reprints are available.

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A.O.A. ACTIVITIES

A Message from the President of the American Osteopathic Association

▶ There has never been a time in the more than 60 years of our existence as an organized profession that we have not had to face major problems. The resolute determination of our predecessors to meet each challenge developed and strengthened this profession. Decade after decade, we have improved our educational facilities, the quality of our faculties, the practice laws of the states, and, what is most important, the quality of medical service our members have provided to patients.

Today, we as members of the profession, have equally difficult challenges to meet. This is only fitting, for without problems, we do not progress, we do not continue our self-improvement as individuals and as a profession. I am *glad* that we face difficult problems. I *welcome* the opportunity to work with the members of my profession to find a solution for each problem as it arises. Therein lie the exciting opportunities offered us.

Many matters demand the highest thought and effort on the part of our National Association, our divisional societies, and our colleges, and of you, as an individual member. There is neither space nor time even to outline here the many matters which at all levels are of concern to us. I can assure you, however, that they all are being met in the spirit of confidence and wisdom for which this profession has always been noted.

Our progress has been phenomenal—absolutely phenomenal! When I think of the expansion accomplished by our colleges, of the many fine osteopathic hospitals built during the last 10 years and now serving the sick and injured of our nation, of the unparalleled loyalty of the thousands of members of this profession as evidenced by the Osteopathic Progress Fund for many years, and now through the support-through-dues programs in twenty-eight states; when I reflect on the sacrifices made by hundreds of my colleagues in serving at the district, state, and national levels on committees and as officers; when I consider the many members of my profession who have forsaken private practice to spend their lives in the service of the profession as teachers in our colleges; when I sit in my study in the evening and ponder the meaning of this profession, not only to its members and their families, not only to our many employees in the offices, clinics, hospitals, and

colleges, but to all mankind—in those moments I know a reverence and awe seldom experienced by the human heart and soul.

Would that I could convey to you my humble thanks for the privilege of being a member of this profession! The problems which seemed so great a moment before are reduced in their size when I consider the strides the profession has made, is making, and will make in the years to come. But each problem, large or small, demands attention. It must and will be solved.

Tonight, here in my study, preparing what I hope will be a *President's Message* which will have significance not only for today, but for our future as well, I approach the task with some trepidation—not for the profession, but for my ability so to order my words that they will convey my thoughts with the clarity the subject demands.

For many years, occasional statements have appeared in the press discussing the possibility of absorption of the osteopathic profession by the American Medical Association. These articles, and the discussions they have occasioned, have increased in frequency and have caused some concern among our members, college students, and faculty members. No matter how baseless the statements or improbable such an eventuality, the concern has been created.

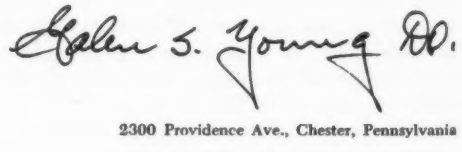
The American Osteopathic Association has repeatedly asserted that it will remain a separate and independent school of medicine. This proposition was reiterated in July of 1959, at the annual meeting of our House of Delegates. This is the established policy of our profession, one which meets with my complete and wholehearted approval. Yet, I fear, and with some justification, that there may be some few among us who have not considered the problem as thoroughly as it deserves.

It is to this matter that I wish particularly to address myself in this and succeeding months. My hope is that I can so express my thoughts that there can and will no longer be any doubt of the wisdom of our course of action. My hope is that these thoughts, in some part the fruit of talking with many people in my travels as President, may find agreement in the hearts of most of us, and solidify the thinking of those who continue to interrogate.

As members of this profession, we have so much in common that we tend to magnify the size and importance of our differences. We have a common purpose in life. This must be kept foremost in our thinking. We must so solve all subsidiary problems that our common purpose will not be lost in the conflict of ideas.

Our common purpose is to provide at all times the best possible quality of health care to our patients. Our every act must be guided by this purpose. This requires concerted action on many fronts. We must maintain ever better colleges, that we may meet the demand for physicians; construct and staff hospitals; conduct intern training programs; provide training programs for every type of specialty practice. By postgraduate education we must maintain our educational standards throughout our professional lives. We, collectively as a profession, must remain active in public health affairs.

In these and other endeavors, much can be accomplished through our organizational strength. But all that we plan or do must have one unwavering, constant purpose—the health care of the people of this nation and the world.



2300 Providence Ave., Chester, Pennsylvania

Alaska and osteopathy

▶ Now that Alaska has become the newest and largest state of the Union, its opportunities and problems have become an integral part of those of the nation as a whole. Primary among the problems in Alaska, even more than in the older states, is caring for the health of its citizens. Alaska does not have enough physicians. It does not have enough hospitals.

While visiting Alaska in the late summer, two osteopathic doctors decided to appraise the part the osteopathic profession might play in this situation, how it might help meet this need and opportunity. They were Dr. Hobert C. Moore, Bay City, Michigan, former A.O.A. President, and Dr. Eugene D. Mosier, Puyallup, Washington, a member of the A.O.A. Board of Trustees. These two doctors visited Alaska's principal cities, conferred with state health and welfare administrators, and visited hospitals and two universities. They met and talked with many citizens. Their interest was to learn how the osteopathic profession may best proceed in carrying osteopathic health care to this new state. Here in part is their account of the trip:

Alaska's problems unique • All problems in Alaska must be considered and eventually solved in relation to the strangely unique character of Alaska itself. Last January when Alaska became the forty-ninth state, it brought to the Union one-fifth of the total area of all the other states—an area of 586,400 square miles—and a civilian population of some 200,000. Of these 35,000 are Eskimos and Indians who are voting citizens, but are under the health care of the United States Public Health Service. This population figure is double that of 1940. Military personnel in Alaska numbers 50,000 or more.

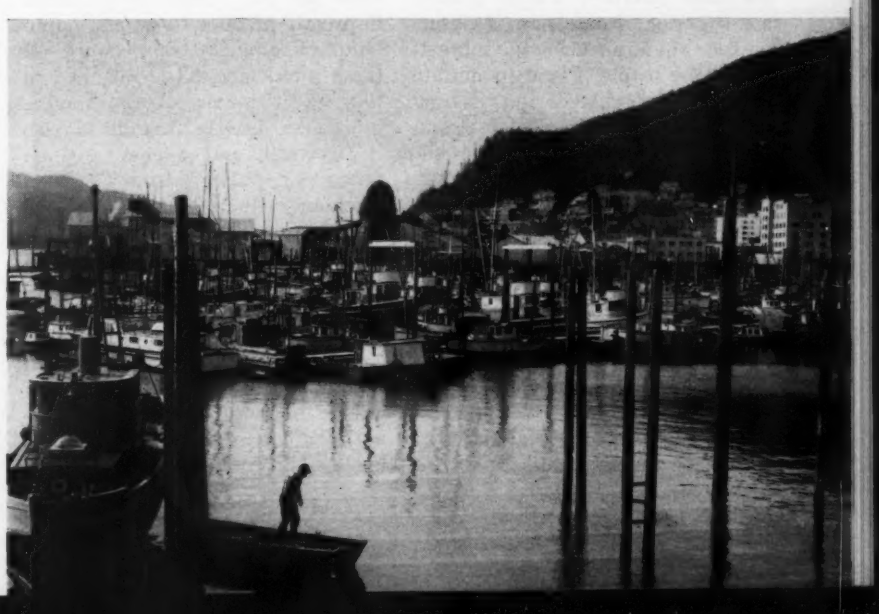
Alaska offers thirty-one of the thirty-three strategic minerals, plus rich oil lands that are only now being developed, natural gas, and hopes of tremendous hydraulic power.

The state is vast beyond description. It stretches from the border of the Canadian northwest into the Eastern Hemisphere. The Aleutian Islands extend beyond the 180th meridian to about 172 degrees east longitude. There are expanses that have never been charted or named, and according to authorities, places where men have not penetrated. In this vastness one finds the modern cities of Anchorage, Juneau, and Fairbanks.

Weather rules • The railroad ends at Fairbanks. Highways are few, so waterways and planes make up the travel arteries. There is one plane for every 150 people, and in remote villages the bush pilot plays an important role in daily life. He flies his plane when all commercial flyers are grounded. Weather rules in Alaska. Conversation is dominated by it, and all things move according to its changes. Despite its inclemencies, however, the bush pilot carries the mail, brings news and color from the outside world, and operates a taxi service, especially for doctors, nurses, and patients going in and out of the bush.

When weather makes it impossible for even a bush pilot to fly, the short-wave radio takes over. All remote villages have a receiving and sending set. This is necessary for survival. It is the only contact with civilization, and the only hope in time of disaster. Evelyn Stefansson, authority on Alaska says, "By means of radio medical information is dispensed to isolated villages. Operations have been performed by school teachers and others with little or no knowledge of surgery. Step by step this is done according to instructions from a doctor perhaps a thousand miles away. Countless babies have been delivered by this hospital of the air waves."

Changing economics • The economic situation in Alaska is changing. Gold mining, which brought



Harbor at Ketchikan, one of seven Alaska towns to boast resident doctors. Alaska has 100 private physicians for 200,000 people

A.O.A. meetings in Central Office

The following meetings of A.O.A. agencies will be held in Central Office in the coming weeks:

Society of Divisional Secretaries	February 6-7
American Association of Osteopathic Examiners	February 7
Conference on Research	March 5-6
American Osteopathic Hospital Association	April 15-16

the rush of 1896, is almost at a standstill because now gold mining does not pay. But there is still plenty of gold to be mined. In dollars, fishing is the largest enterprise, although the Alaskan names the defense industry as most important. This employs thousands of Alaskans and has brought in many skilled workers. In the southeast, there is a large pulp industry. Fast becoming big business today is the tourist trade. Building adequate accommodations for tourists may be expected to boost business. Business men feel, however, that without the defense industry Alaska's economy as a state would be shaky. Thus to insure progress, the state needs more permanent settlers and an influx of capital.

Land of youth • Alaska is the land of youth. The average age of its citizens is 26 years. The birth rate is high and the death rate low. The young people are vitally alive and concerned about providing the best for their families. Public schools are superior. Recreation is unsurpassed. Modern Anchorage is bursting at the seams. Planes penetrate the remotest villages, an Eskimo boy flies a thousand miles to attend school in Sitka, a thousand children fly to school every day.

In the areas of the Eskimo and Indian, the U.S. Public Health Service does an excellent job in general health and dental care. But health care in general is seriously inadequate. Frequently, as in the widely publicized illness of Alaska's Governor William Egan last year, the critically ill are flown to the "old country." Dental and other health appointments in Seattle or Portland are routine. Even in the cities of Juneau, Anchorage, Seward, and Fairbanks the demand for hospital care far exceeds the supply. From the remote areas, patients are flown to the already crowded hospitals or to the "outside."

In some measure, the situation is alleviated by the medical care supplied by the military bases. With more than 50,000 personnel in the Armed Forces, there are enough military physicians to supply care for the military and for the thousands of civilian employees. Without the help of these military physicians, and that of the U.S. Public Health Service, the health care situation would be even more serious.

Distribution of doctors • The vastness of Alaska will always make a proper distribution of doctors difficult. An increase in their number will, it is believed, depend to some extent on the economic growth of the state. In Alaska now there are 101 doctors of medicine in private practice to serve a population of some 200,000 persons. Of these physicians, 83 are located in the seven towns of Anchorage, Fairbanks, Juneau, Ketchikan, Sitka, Seward, and Spenard, which range in population from 11,250 in Anchorage to 2,108 in Spenard. This leaves 18 medical doctors for some 175,000 persons, although several thousand of these receive care through governmental medical plans. One D.O. is in practice in Anchorage.

There is a shortage of nurses and related medical auxiliary personnel. The cost of living is high. Living costs in Anchorage are estimated to be 39 per cent higher than in Fairbanks, and 54 per cent higher than in Seattle. As a result, the doctor's expense is also high. Secretarial help is expensive, and rent and construction cost are about one-third more than in the Pacific northwest.

As mentioned, the median age of the population is 26, with an annual birth rate of 35 for every 1,000 population. This compares with the general U.S. birth rate of 25 for every 1,000 population.

12,000-word Constitution • The Constitution of Alaska was adopted by the voters on April 24, 1956, some 3 years before the territory became a state. The Constitution is brief. It contains 12,000 words, as compared with the Constitution of Louisiana which contains 201,423. Perhaps its outstanding characteristic is its provision for an extremely strong executive branch of government. The governor is the only independently elected state officer, and serves a 4-year term.

A unique feature of the state office set-up is that the Secretary of State succeeds to the Governor's office in the event of a vacancy. The candidates for the office of Secretary of State are nominated at the primary election, as are other candidates. At the general election, however, a vote for the Governor is considered a vote for the Secretary of State running with him. Thus the Governor and the Secretary of State will always be of the same party. Executive departments are limited to 20 in number and are now organized under an administration act approved by the legislature in 1959. Heads of the various departments are appointed by the Governor and confirmed by the legislature. The head of each department, as is specifically provided in the Constitution, "shall serve at the pleasure of the Governor." Thus though the head of a department must be confirmed by the legislature, he may be removed from office at any time by the Governor.

Territorial laws continue • The territorial laws in effect at the time that Alaska became a state, as provided by the Act of Admission approved by the United States Con-

gress and by the people of Alaska, "shall be and continue in full force and effect throughout said state except as modified or changed by the legislature of the state at a later date." The first session of the Alaska legislature met in early 1959 and will meet in annual sessions hereafter.

There are three laws which can relate to the practice of osteopathy in the state. One is the Basic Science Act which was originally enacted in 1946. This is similar to the basic science laws of other states. It specifically relates to "the practice of osteopathy" in addition to other schools of practice. Section 2 of the Act provides that one of the members of the board of examiners in the basic sciences shall be a doctor of osteopathy. No D.O. is now serving on this board.

No reciprocity for D.O.'s • In the administration of the basic science act the board of basic science examiners has taken the position that a basic science certificate from one of the other basic science boards presented by a D.O. may not be accepted for reciprocity or endorsement because no other law of the state provides for the examination and licensing of doctors of osteopathy. Thus in order to procure a basic science certificate, a D.O. must now take the examination of the board of examiners in the basic sciences in the prescribed subjects of anatomy, physiology, pathology, bacteriology, hygiene, or chemistry.

Separate professional licensing acts have been enacted to regulate the practice of medicine and the practice of chiropractic. The board of medical examiners takes the position in the administration of the Medical Practice Act that the Act is not applicable to doctors of osteopathy. Thus the board of medical examiners will not accept applicants holding the D.O. degree. This ruling merits further study.

Business License Act • In addition, however, to the Basic Science Act one other statute may be applicable to doctors of osteopathy. This law is the Alaska Business License Act under which doctors of osteopathy and others engaged in business must apply to the Alaska Department of Taxation and procure an annual Alaska Business License. The annual tax is $25.00. The continued absence of a professional licensing law, whether it be a part of the medical practice act or a new independent osteopathic practice act, makes the present legal status for doctors of osteopathy in the state unsatisfactory. The exact scope of lawful osteopathic practice is not clear.

It is believed, however, that there is interest on the part of the state government, the legislature, and state officials in seeing to it that health services in Alaska are provided upon the same basis as are health services in the other forty-nine states. The unlimited licensing laws in other states, information on the six colleges of osteopathy, the general hospitals staffed by doctors of osteopathy, and similar basic professional information were made known to state officials whenever possible. Thus the type of information needed to create an interest in providing for a better regulation of the practice of osteopathy in the state was made available.

Problem is lack of information • The problem of Alaska, therefore, can be said to be not unlike those of the few other limited practice rights states, where there is a general lack of information concerning osteopathy, its character, services, and professional training program. As in these other states, there are not enough D.O.'s to make these matters known to the public and the state government.

Statehood will not solve Alaska's economic, social, health, and other difficulties overnight. This visit to Alaska indicated, however, that the osteopathic school of medicine could help meet the needs for health care in the state if members of the osteopathic profession were granted, under an appropriate licensing law, a legal status equal to that provided under the Medical Practice Act for doctors of medicine. The fact that the neighboring state of Washington provides under its Osteopathic Practice Act for the unlimited licensing in practice of doctors of osteopathy should be a help in this regard because of the close relationships between Alaska and Washington. The Washington Osteopathic Association has already taken an interest in this subject, and, it is believed, will be extremely helpful in bringing about a solution to this important problem facing both Alaska and the profession. Likewise, Alaska and the state of Oregon have a close relationship developed over the years. The unlimited licensure of the profession in Oregon should also be persuasive.

The problem of Alaska is one to command the interest of the entire profession, and to engage general cooperation in doing whatever is possible to help meet the health needs in the new state.

Eskimos hitch their dog teams at Kotzebue, more than 100 miles north of Nome. Alaska adds an area of 586,000 square miles to the United States

Bureau of Public Education on Health

Illinois Medical Practice Act Amended

▶ The 1959 Session of the Illinois State Legislature brought the first important amendments to the Illinois Medical Practice Act since 1923 insofar as it applies to doctors of osteopathy in practice. Senate Bills 723 and 724 were enacted into law, and constitute important legislative changes.

Senate Bill 724 amends Section 60a of the Civil Administrative Code to provide that the Medical Examining Committee of the Department of Registration and Education, which administers the Medical Practice Act, be increased from five to seven members. It also provides that one such member "shall be a reputable licensed physician possessing the degree of doctor of osteopathy." Previously the Medical Examining Committee was made up of M.D.'s.

Even more significant was the enactment of Senate Bill 723. This amends the Medical Practice Act to provide a statutory means for a doctor of osteopathy licensed in the state for not less than 1 year prior to July 8, 1959, and who holds a license to treat human ailments without the use of drugs or operative surgery, may qualify for a license to practice medicine in all its branches. At the time of the enactment of the law only graduates of the Chicago College of Osteopathy since 1949 were being admitted to the examination of the Department of Registration and Education for a license to practice medicine in all its branches. Under this new law such doctors as complete the required postgraduate education and successfully pass the examination in the required subjects will be issued a license to practice medicine in all its branches in Illinois.

The Chicago College of Osteopathy is already engaged in conducting the first postgraduate course under the law. Over 140 doctors have registered at the College to take this course.

The text of the new law follows:

Section 13.1. Persons licensed prior to 1959—Effect—Post-graduate work. Any person who holds, on the effective date of this amendatory Act of 1959, a valid and existing license under Section 11 Paragraph 2 of this Act, and who has been a resident of Illinois and has been engaged in practice pursuant to such license in Illinois for not less than one year prior to such effective date shall, upon proof of successful completion of a post-graduate course meeting the requirements of this section in materia medica, therapeutics, surgery, obstetrics, and theory and practice, upon application to the Department of Registration and Education, prior to July 1, 1963, be permitted to take the regular examination in those subjects. Upon receipt of a passing grade in such examination, such person shall receive a license to practice medicine in all its branches. If an applicant shall already have a license to practice obstetrics he shall not be required to take the course or examination in that subject.

The post-graduate course referred to in this section may be taken only in a school or college located in Illinois which is reputable and in good standing, in the judgment of the Department, for the training of applicants for, or the post-graduate education of persons already holding, a license to practice medicine in all of its branches. Such course shall include a total of 248 hours of classroom and laboratory instruction (except that a credit of 24 hours will be allowed those applicants already holding a license to practice obstetrics) and post-graduate students taking it shall be required to be in actual resident attendance while taking the course. Such course shall be the same in content as the regular courses in these subjects offered by such reputable school or college. (Section 13.1, Chapter 91, Smith-Hurd Illinois Statutes Annotated; July 8, 1959, Illinois Laws 1959, S.B. No. 723)

Bureau publishes 1960 public health booklet

▶ In the mail the first week of January was the "1960 Public Health Information Booklet," produced by the Bureau of Public Education on Health, of which Dr. Eugene D. Mosier, Puyallup, Washington, is chairman. This second edition is being distributed to A.O.A. trustees, and to divisional society presidents, secretaries, and legislative chairmen. It is available upon request to members of the Association. The first edition was published in 1955.

The publication is made up of seven sections: public education on health; medical education; state licensing and regulation; hospitals and practice; other health organizations; health insurance and medical economics; and national interprofessional code for physicians and attorneys.

As President of the American Osteopathic Association Dr. Galen S. Young is scheduled in the coming months to attend these conventions and meetings:

American College of Osteopathic Obstetricians and Gynecologists and American College of Osteopathic Pediatricians, San Antonio, Texas, February 21-25

Colorado Osteopathic Association, Colorado Springs, March 31-April 3

Texas Association of Osteopathic Physicians and Surgeons, Dallas, April 27-30

Minnesota State Osteopathic Association, Minneapolis, May 5-7

Indiana Association of Osteopathic Physicians and Surgeons, Indianapolis, May 15-17

Virginia Society of Osteopathic Physicians and Surgeons, Williamsburg, May 27-28

Social Security Disability Program

▶ The House Ways and Means Committee Subcommittee on Administration of the Social Security laws held open hearings on the OASI disability program off and on during November and the first part of December.

As a result of the hearings, Subcommittee Chairman Burr P. Harrison of Virginia announced his intention to sponsor legislation at the opening of the January 1960 session of Congress to repeal the requirement that an otherwise eligible person must be at least 50 years old before he can qualify for disability benefits. Subsequently, House Ways and Means Committee Chairman Wilbur D. Mills of Arkansas included such a proposal in his list of examples of Social Security legislation his Committee will probably consider during the 1960 session of Congress.

A.O.A. statement • Following is the statement of the American Osteopathic Association before the Subcommittee on the Administration of the Social Security Laws on the Social Security Disability Program House Ways and Means Committee. It was submitted by Dr. Chester D. Swope, Chairman, Council on Federal Health Programs, on November 12, 1959:

Mr. Chairman, your letter of invitation to the American Osteopathic Association to offer suggestions for consideration by your Subcommittee on Administration of the Social Security Laws led to our survey of the principal officers of the state osteopathic societies, and the resultant consensus was that the Bureau of Old-Age and Survivors Insurance is doing a good job of administering the Social Security disability program.

In cooperation with BOASI we have published articles in THE JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION, a monthly publication supplied to all our members, pointing up the responsibilities of attending physicians and hospitals in rendering complete medical reports and other acceptable medical information when called upon by their patients who are applicants for Social Security disability benefits.

Both the disability "freeze" provisions which were added to the Social Security Act in 1954 and the disability insurance program incorporated in the Act in 1956 involve the attending physician's evaluation of permanent physical or mental impairment.

The State agency (usually the State rehabilitation agency) which, under agreement with the Federal Government, makes the determination of permanent disability including both medical and socioeconomic evaluations, may consider it desirable to verify the interpretations placed on the medical findings by the claimant's sources or may desire a consultative examination to reconcile what appear to be conflicting findings in several reports.

The claimant's attending physician may, upon request, receive a copy of the report of the consulting examiner.

Consultative examinations are made by specialists picked by the state agency. The expense of consultative examination is borne by the Federal Disability Insurance Trust Fund, whereas the current examination, if any, by the claimant's physician is the responsibility of the claimant. According to BOASI, consultative examinations are being used in about one third of the disability claims processed.

Sometimes, in order to save the expense of laboratory and other costs of examination or because of inability to defray these costs, patients will mail the medical report forms to their attending physicians and the forms must be completed on the basis of past records without the benefit of current examinations.

It should reduce the number of the more expensive consultative examinations and shorten the processing time, if as a charge against the Trust Fund claimants were enabled to obtain current examinations from their attending physicians so that the information could be included more fully in the initial medical report.

The Subcommittee is to be commended for its watchful interest in reference to this program and its staff is to be complimented on the Fact Book of invaluable information on the program.

We appreciate the privilege of submitting our comments.

Council publishes state manual, booklet on estates

▶ Two publications have just been released by the Council on Development. The first, "How to Plan Your Estate," provides information on wills, trusts, and gifts. A number of tables demonstrate the impact of our tax system on estates, and suggest methods by which tax loss may be reduced.

The booklet is a condensation of the series of articles that appeared last year in THE FORUM OF OSTEOPATHY, June through October. They were prepared by Mr. Lloyd L. Hall, Topeka, Kansas, chairman of the Council's Subcommittee on Estate Planning. Mr. Hall is executive secretary of the Kansas State Osteopathic Association.

Second of the releases is the "Manual for State Councils on Development," produced by the newly appointed Committee on State Development Councils, of which Dr. George W. Northup is chairman. It has been supplied to all members of the National Council, divisional society secretaries, college presidents, and members of the present nineteen state councils on development. It will be supplied to new councils as they are organized.

The handbook is primarily for members of state councils. It treats fully the purposes, structure, and committees of the National Council, suggests methods of adapting, in whole or part, the same set-up to divisional organizations.

The Committee on State Development Councils, also designated as the Committee on Divisional Societies, was appointed at the November meeting of the National Council by Council Chairman, William B. Strong. The nineteen states that have so far formed councils are California, Colorado, Florida, Indiana, Kansas, Kentucky, Maine, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Ohio, Oregon, Pennsylvania, Texas, Vermont, Washington, and West Virginia.

HEADQUARTERS ACTIVITIES

Leonard Heffel

Tom Dominick resigns; P.&P.S. gains new writer

▶ Two Central Office staff changes have been announced within the month by Executive Secretary True B. Eveleth. Thomas S. Dominick resigned on December 15 as assistant to Business Manager Walter A. Suberg, and on January 4 Leonard Heffel became a member of the staff of Public and Professional Service.

Mr. Dominick had been with the Association since 1951, and for the last 3 years had worked with Mr. Suberg in all areas of personnel and business management. He left to take a position with the Alexander Proudfoot Company, Chicago, consultants in business management.

Mr. Heffel comes to the Association as a staff writer for the Division of Public and Professional Service, from 2 years as chief of the Chicago Bureau of *Scope Weekly*.

He received his training at the University of Wisconsin, and holds a Bachelor's degree in English and Education and a Master's degree in Journalism. During his graduate study, he served as a medical writer for the University of Wisconsin news service, and in public relations for the University hospitals. His 2-year military service was spent in Alaska.

Mr. Heffel is 28 years of age, is married, and lives in Evanston.

Staff travels

▶ Five members of the Headquarters Staff represented the National Association at these meetings during late December and January:

Robert A. Klobnak, director, Division of Public and Professional Service, and Otha W. Linton, press representative, attended the annual meeting of the American Association for the Advancement of Science, held in Chicago December 26-30. Mr. Linton also attended the meeting of the A.A.A.S. affiliate, the National Association of Science Writers, of which he is a member.

Mr. Klobnak, as a staff consultant of the A.O.A. Council on Development, was present at the organizational meeting of the Florida Council on Development, held in Tampa January 9.

Lawrence W. Mills, director, Office of Education, was the banquet speaker at the January 9 meeting of the Dade County Osteopathic Medical Association, held in Miami, Florida. Mr. Mills also visited two osteopathic colleges January 10-14, the College of Osteopathic Medicine and Surgery, Des Moines, Iowa, and the Kansas City College of Osteopathy and Surgery, Kansas City, Missouri.

Robert Bennett, director, Osteopathic Progress Fund, attended the annual meeting of the Massachusetts Osteopathic Society, held January 16-17 in Boston.

California and Michigan lead in seal campaign

▶ The December 31 report on the current Christmas Seal campaign shows a total return of $33,500, slightly above returns of the same date last year, according to Mrs. Alyce Balfour, campaign secretary.

Among the states, California and Michigan are leading, California with a year's end total of $3,165, and Michigan with $2,885. The other eight of the ten leaders, according to Mrs. Balfour, are Ohio, Pennsylvania, New York, Illinois, New Jersey, Indiana, Texas, and Massachusetts.

Among the osteopathic colleges, the Kansas City school leads with an all-time college high of $1,670. This was raised by the joint efforts of the students and the student wives' group.

Alyce Balfour, secretary of the osteopathic Christmas Seal program, tallies state totals from packets of envelopes. California and Michigan lead among states, with Ohio and Pennsylvania third and fourth in seal totals. Campaign as whole keeps pace with returns of last year